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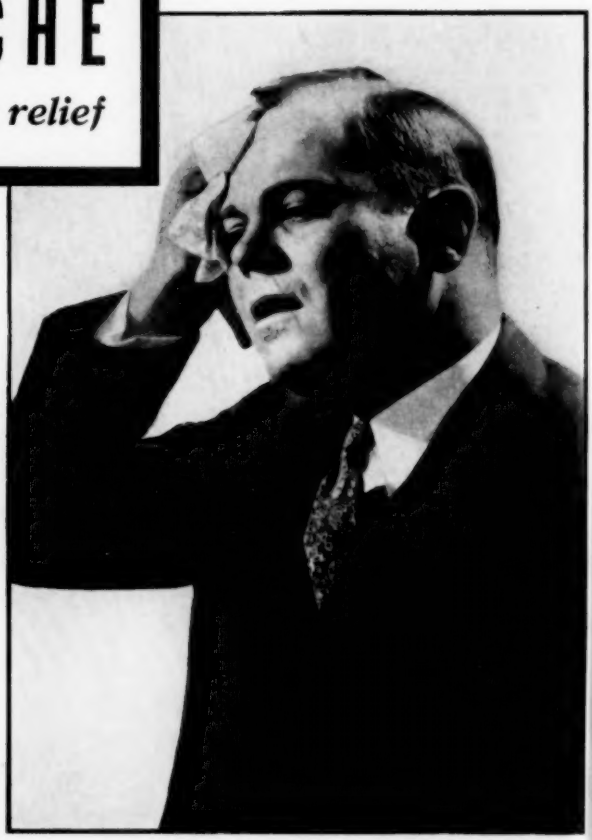

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JULY, 1938

ORIGINAL ARTICLES.

THE EVOLUTION OF THE PARENCHYMAL LUNG LESIONS IN RHEUMATIC FEVER AND THEIR RELATIONSHIP TO MITRAL STENOSIS AND PASSIVE CONGESTION.

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Cardiac involvement is the main object of interest in rheumatic fever to both the clinician and pathologist. There is often, however, a pulmonary change in that disease that is in many respects equally important and indeed responsible for some of the signs and symptoms that have been attributed to the heart itself.

This report deals with the evolution of the pulmonary lesions of rheumatic fever, tracing the relationship of the acute pneumonia or pneumonitis to the chronic pathologic changes seen in the lungs of patients who have mitral stenosis and other evidences of advanced rheumatic heart disease. This study was undertaken in connection with the larger problem of the possible influence that such pulmonary changes might have on the evolution of rheumatic heart disease. We do not believe that the pulmonary changes in late rheumatic heart disease are to be ascribed wholly to congestive failure. Contrariwise, we are led to believe that these can be attributed in major part to recurring inflammation, such as may be seen in the heart in the prolonged course of rheumatic disease.

The pulmonary lesions of rheumatic fever are: 1, the parenchymal; 2, the vascular; 3, the pleural. We deem the first two important in the development of the chronic cardiopulmonary state of rheumatic disease. Pleuritis is a common feature but probably

has little influence on the course of cardiac disability, except in those uncommon instances where adhesion is complete and bilateral.[12] It is therefore only briefly mentioned and the reader is referred to Paul's[10] work for detailed discussion. The lesions should be further divided into: 1, acute; 2, subacute; 3, chronic.

The Acute Phase of Rheumatic Pneumonopathy. The clinical aspects of the pneumonia and pneumonitis[5a] will not be repeated in this report, but the pathologic changes will be reviewed and certain features discussed in detail because of their importance as connecting links in the transition from the acute inflammatory to the late chronic stages of the pneumonopathy. This acute lung lesion is an interstitial hematogenous inflammation having the same pathogenesis as carditis and arthritis. It varies greatly in severity and extent, appearing in some instances as small isolated foci of hemorrhagic pneumonitis and in others as a widespread pneumonic consolidation. The lower lobes are usually more extensively involved but the upper lobes may be equally affected; the process is generally bilateral and commonly extends in a "wandering" transient manner.

Congestion and hemorrhage are often striking features contributing not only to the consolidation proper but giving it a richly varied color—dark red, occasionally a deep purplish-blue, contrasting with the pallor of adjoining uninvolved areas or the rusty-brown of subsiding congestion. Numerous small hemorrhagic foci are often scattered over the non-consolidated areas and have the same essential relationship to the rheumatic process as the major lesions of pneumonitis and consolidation. Although an entire lower lobe may be involved, consolidation is usually not so bulky as that of pneumococcic pneumonia; more often it is incomplete, excised sections showing a variable tendency to sink in water or to do so slowly. Section reveals a deep red or reddish-brown parenchyma with a smooth almost non-granular surface and liver-like consistency. In the past, this consolidation has been most often regarded as an atelectasis; the latter often does develop as a later complication. Rheumatic pneumonitis is essentially a non-suppurative lesion. The bronchial mucosa is congested but generally free of purulent exudate; empyema or abscess are rarely seen, then only because of secondary infection.[6]

There are variations from the typical picture that are worthy of brief comment. In some cases of fulminating rheumatic fever, pulmonary congestion with hemorrhage are so marked as to obscure the inflammatory features of the lesion. Striking examples in children were described by Coburn.[2] Lesser grades of congestion are commonly noted and often regarded merely as acute passive hyperemia, incidental to heart failure. The hemorrhagic factor occasionally leads to an atypical infarction, a dark red, poorly demarcated consolidation, not having the classical wedge or triangle

shape, the dry appearance or necessarily the subpleural localization of the ordinary infarct. It may pass for rheumatic pneumonia (of which it is usually a part) and is identified usually by histologic examination which further reveals its atypical nature.

The Histopathologic Change in Acute Rheumatic Pneumonopathy. The acute interstitial inflammation in the rheumatic lung is seen as a thickening of the alveolar walls through capillary congestion, edema, focal necrosis and cellular infiltration. The capillary congestion is often intense and accompanied not only by edema of the septa but by escape of fibrin to the alveolar spaces causing further consolidation of the tissue. The inflammatory reaction may be conveniently divided into three stages: 1, destructive; 2, proliferative; and 3, reparative.

The initial destructive phase is characterized by foci of fibrinoid necrosis in the alveolar walls with cellular infiltration of monocyte variety, apparently of reticular and endothelial capillary origin.* These cells, deeply stained, are of various shapes, often fragmented and usually associated with sparse numbers of similarly fragmented neutrophils (Figs. 1 and 2). The fibrinoid necrosis while usually focal is occasionally widespread, involving the entire wall of an alveolus or of contiguous alveoli, with marked destruction of the elastic and reticular framework. In severe cases of rheumatic pneumonia the alveolar walls may be converted literally into "ribbons" of fibrin (Fig. 3). The congested capillaries often undergo a hyaline thrombosis and lose their integrity. Cellular infiltration into the alveoli is usually scant, consisting of phagocytes, desquamated alveolar cells and occasional neutrophils. Dense infiltration of the latter is uncommon.

The second or proliferative phase is marked by the infiltration of larger basophilic cells, often with vesicular nuclei, sometimes multinucleated; they are the so-called "Aschoff" cells, often in perivascular groups, spreading out into the interstitial tissues, not subject to the necrosis and fragmentation described above and apparently replacing the initial cellular invasion.

The third stage, which we assume to be a reparative reaction, consists in the presence of infiltrated plasma cells and lymphocytes, and proliferated fibroblasts. Elaboration of collagenous material by fibroblasts becomes more and more evident. These changes often coëxist in the same section blending into each other with little or no demarcation. At times the intermediate or proliferative reaction is apparently slight, the reparative process following quickly on the initial destruction.

The Aschoff nodule common to the myocardium is seldom encountered in the lung; however, the fundamental morphologic changes

* The term "epithelioid" formerly applied to this monocytic infiltration has been discarded; its use had been suggested by the resemblance of the early monocytes to those of tubercle and other granulomas; they probably have a similar origin.

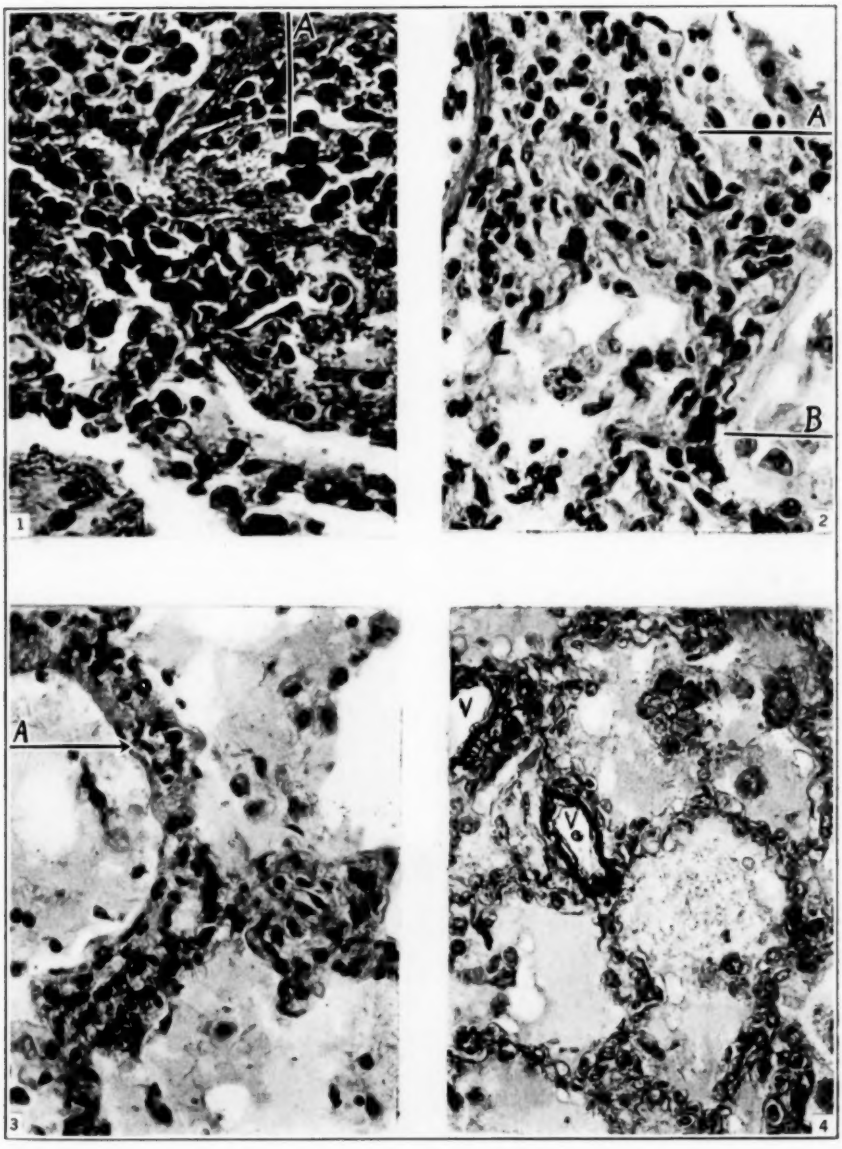
inherent in the formation and "life cycle" of the classical nodule are all seen in the interstitial pneumonia of rheumatic fever, namely, the initial focal fibrinous (fibrinoid) necrosis, the later proliferative infiltration of macrophages, the final fibrosis. The interstitial structure of the lung possibly does not lend itself readily to the formation of nodules. It is not uncommon, however, to find seminodular perivascular aggregations of macrophages, and in some cases characteristic Aschoff bodies were noted, not merely in the subpleural tissue[4] but in the lung parenchyma.[6] An exhaustive search through a number of sections would probably reveal their presence in greater number than heretofore described.

Variations in the histologic picture correspond to those noted in in the gross. Often the marked congestion obscures the other inflammatory aspects, but it differs from the purely passive hyperemic state in that it is accompanied by marked hyperplasia of the capillary endothelial and interstitial reticular cells and their migration in large numbers into the tissue spaces. In many instances, marked congestion, the presence of so-called "Herzfehler Zellen" and undue reticulo-endothelial cellularity are at first glance the only changes noted in the acute rheumatic lung lesion. Continued search, however, will usually show foci of early fibrinoid necrosis, with cell fragmentation.

"Inflammatory Infarction" in Rheumatic Pneumonia. In ordinary infarction, a mere skeletal framework of the alveolar structure remains unaccompanied by any viable cell structure. We have noted infarction on 6 occasions in rheumatic pneumonopathy where the interstitial tissue was tremendously thickened by fibrin and cellular exudate, the new cells maintaining some degree of viability. Obliterating rheumatic arteritis is usually a part of this lesion.

The Destruction of the Elastic and Reticular Network. The destruction of the normal elastica, probably common to many types of pneumonia, seems of greatest significance in the rheumatic pneumonopathy where the inflammation is primarily interstitial and featured often by necrosis. The normally delicate elastic fibers are broken and disintegrated, appearing in the Weigert stained preparation as fragmented threads or as irregular dots, in many places being quite lost (Fig. 4). This is apparently the basis of the subsequently impaired elasticity of the lung tissue following rheumatic pneumonitis.

The Subacute Phase of Rheumatic Pneumonitis. The subacute phase is a continuation of the reparative process just described. It is featured by: 1, Marked changes in the consistency of the involved lung tissue; and 2, basal atelectasis (inconstant). The subacutely inflamed lung, although not consolidated, remains poorly aërated and often should a whole lobe or a large part of one be involved, is somewhat smaller than normal. The color varies from dark red to reddish (rusty) brown and the subpleural lymphatics



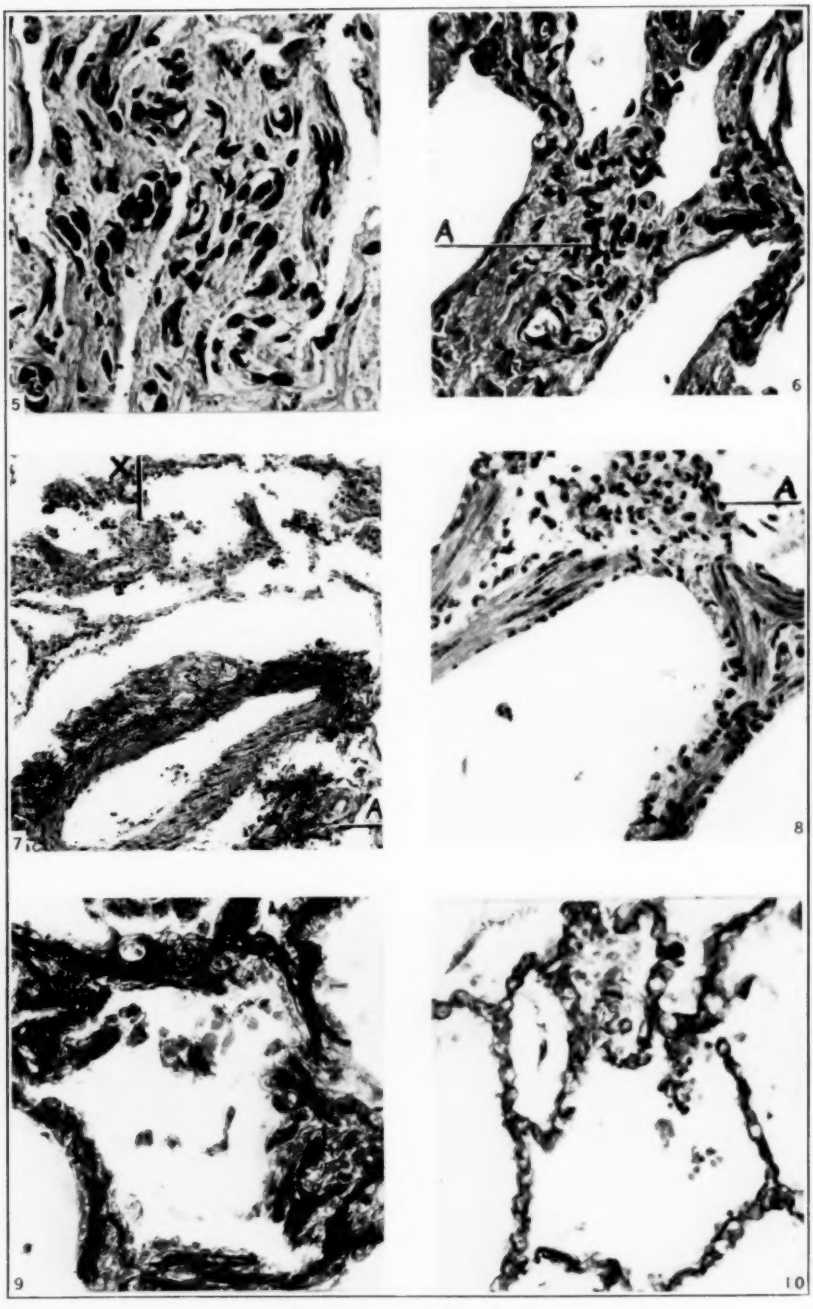
A *B*

FIG. 1.—Acute rheumatic pneumonitis; dense focal infiltration of monocytes, including large multinucleated Aschoff cells (*A*) in a focus of "fibrinoid" necrosis, with obliteration of the alveolar structure (× 552).

FIG. 2.—Acute rheumatic pneumonitis; fibrinous swelling and necrosis of alveolar wall with seminodular infiltration of monocytes of varied shape and size, some of them fragmented (*A*). An occasional polymorphonuclear and lymphocyte are seen; also larger deeply stained multinucleated cells (*B*) (× 460).

FIG. 3.—"Fibrinoid" necrosis of alveolar walls in acute interstitial rheumatic pneumonitis (*A*) (× 368).

FIG. 4.—Destruction of interalveolar elastica in acute rheumatic pneumonitis. Small shreds and dots of elastica remain; it is better preserved in the small blood-vessels (*V*).



FIGS. 5, 6, 7, 8, 9 and 10.

are often prominent as a gray web. The pleural surface may show localized plastic pleurisy, and easily broken fresh adhesions are often seen laterally and especially in the interlobar fissures. Small to moderate-sized pleural effusions with increased fibrin content are commonly observed, while hydrothorax of true congestive failure is less often encountered. Section reveals tough lung tissue having a rubberoid consistency, cutting with an increased resistance, the cut edge remaining rather sharp. The cut surface may be moderately moist or in some cases quite dry. Inspection of the pulmonary artery and its larger branches usually reveals nothing of note in young subjects in whom rheumatic involvement has been recent. The striking change from the normal lung lies in the altered elasticity.

Microscopic examination reveals early diffuse interstitial fibrosis, replacing the monocyte-macrophage infiltration (Fig. 5). Often the transition is uneven, there being foci of acute pneumonitis in close proximity to early fibroblastic activity. We wish to emphasize that this fibroblastic process is in direct sequence to an acute inflammatory reaction and not to passive congestion. Marked pulmonary edema is not often noted in these microsections, and usually the congestion associated with acute pneumonitis has already subsided although a certain amount of interstitial edema persists. In many instances, there are numerous "Herzfehler" phagocytes both within the interstitial tissue and in the alveoli. In this subacute phase there is noted the early regeneration of the elastic tissue; the peculiar aspect and probable significance of this regeneration will be commented upon later.

Necropsy in the subsiding phase of rheumatic fever (corresponding with the subacute and subchronic phases of rheumatic carditis and pneumonitis) often reveals characteristic basal collapse or atelectasis, which usually but not necessarily is associated with pleural effusion. The degree of pulmonary collapse occurring with rheu-

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LEGENDS FOR FIGS. 5, 6, 7, 8, 9 AND 10.

FIG. 5.—Subacute phase of rheumatic pneumonitis. Note fibrocytosis and deposition of collagen. There is collapse of alveoli (lobular atelectasis) (× 460).

FIG. 6.—Marked thickening of alveolar wall by collagen in subchronic rheumatic pneumonitis. Note small foci of recurring inflammation (*A*) (× 184).

FIG. 7.—Low-power view of late chronic postrheumatic interstitial pneumonitis. There is marked pulmonary impairment, with irregular fibrotic thickening of the alveolar walls (*X*). An occasional focus of emphysema is noted. A larger muscular branch of the pulmonary artery is normal, while two arterioles (*A*) are slightly to moderately thickened (× 80).

FIG. 8.—Recurring acute rheumatic pneumonitis in late chronic phase of the lesion.

FIG. 9.—Hyperplasia of interalveolar elastica ("pulmonary elastosis") of chronic rheumatic pneumonitis from a patient, aged 37, with mitral stenosis, pulmonary hypertension and cor pulmonale. Death by right heart failure. Note coarse deeply stained and disrupted elastica; Weigert stain (× 230).

FIG. 10.—Control section from normal lung of woman, aged 28; note delicate elastica and normal alveolar structure; Weigert stain (× 276).

matic pneumonitis is sometimes very striking. For many years it has been ascribed to pleural and more often pericardial effusion and localized to the left base. Both Naish[8] and ourselves[5a] have noted that basal collapse can occur as well on the right side. The pleural effusions so commonly seen are mostly of inflammatory origin, and, although coëxisting rheumatic myocarditis is almost inevitable, congestive heart failure is a major factor in only a minority of these patients. We believe that impaired elasticity of the lung is the basis for this atelectasis, and that such altered lung tissue is exceptionally vulnerable to pressure, whether exerted by accumulation of pleural or pericardial fluid or by elevation of a temporarily inactive left diaphragm.[3]

Chronic Stage of Rheumatic Pneumonopathy. Patients dying with chronic rheumatic heart disease, with or without advanced mitral stenosis, show in the large majority a pathologic change in the lung structure. Hitherto the attention of the pathologist has been directed to the presence of hydrothorax, pulmonary edema, infarction and, in view of the recent knowledge of pulmonary arterial hypertension, to the state of the pulmonary arteries which often exhibit considerable atherosclerosis. The lungs will commonly show a denser consistency, and usually remain semi-inflated on removing the chest plate. They may be grayish or else reddened in varying degree by congestion. Old pleural adhesions, basal or lateral, are commonly noted and occasionally the entire lung is covered by thickened opaque pleura. Section will reveal a rather firm inelastic structure in which, with the aid of a hand lens, the alveoli can be seen standing out as a well-supported, somewhat stiffened honeycomb that resists the deflating effect of atmospheric pressure, the result of interstitial fibrosis. In many cases the altered consistency is readily apparent and amounts to a diffuse toughness. In discussing the subacute pulmonary lesion we used the term "rubberoid," which may well be applied to the chronic state. Such lungs are cut with more precision than the normal because of the increased resistance. A certain amount of emphysema is not uncommon to the lungs of the chronic rheumatic state. This is a secondary effect, however, following the interstitial fibrosis and the loss of the normal elastica and is best seen in marginal sites, anteriorly and at the bases; occasionally it is of the advanced "bullous" variety. This increased resistance, the impaired deflation and the secondary emphysema are not limited to the lower lobes, but can be noted as well in the upper lobes, usually however in lesser degree. The fibrosis is sometimes associated with moderate anthracosis, in which event the lung tissue is considerably tougher than is ordinarily seen with the latter condition alone. It may be accompanied by focal induration, usually in the lower lobes and possibly the result of healed infarction or the sequel of previous basal collapse.

The Histopathologic Picture of Chronic Postrheumatic Pneumonitis. Histologic examination of the gray semirigid or "rubberoid" lung will show the alveolar walls thickened with collagenous fibrosis, the extent of which may vary greatly even from field to field in the same section, perhaps involving large areas uniformly. More often a portion of an alveolar septum will be replaced by fibrous tissue yielding in the aggregate a patchy involvement rather than a diffuse and complete interstitial fibrosis. The thickness of the affected alveolar wall is at times extreme, as much as 60 microns. The process was termed pericapillary fibrosis by Moschcowitz[7] and its development around the pericapillary basement membrane rather than along the outer subalveolar membrane was beautifully illustrated by Parker and Weiss.[9] It is often associated with some degree of pericapillary edema which is probably due to compression and localized obliteration of lymphatic and blood capillary network. With marked fibrotic thickening and diminished capillary blood supply there is frequently an associated metaplasia in the alveolar lining cells, the latter becoming cuboidal. This fibrosis following rheumatic pneumonitis is not the same as the carnification or delayed resolution of ordinary pneumonia, in that the process is interstitial and the alveolar spaces are preserved even though focal atelectasis does occur. Small foci of recurring acute pneumonitis are not uncommonly seen in the toughened lungs of patients who have had chronic rheumatic disease of long standing (Fig. 8).

Differential stains (Weigert) show in many instances a marked hyperplasia of elastic tissue in the form of thick, coarse, deeply stained fibers, often irregularly banded, often disrupted and fragmented (Fig. 9). They are most prominent in those alveolar walls that are thickened by collagen fibrosis and appear to be a considerable part of that fibroblastic reaction. This hyperplasia possibly starts as a regenerative process following acute rheumatic pneumonitis in which the normal elastica is largely destroyed; at least, in subchronic phases of the rheumatic pneumonopathy the beginning of the hyperplasia is often noted. The new elastica can apparently be destroyed as was the preceding normal structure by recurring acute interstitial pneumonia. The hyperplasia may develop to a remarkable degree. We have used the term "elastosis" in reference to its histologic picture. It is apparent that this abnormal elastic tissue does not have the functional value of the delicate elastica of normal lung parenchyma. The elastic recoil is lost; there is noted instead on palpation an increased resistance almost reminiscent in some cases of India rubber. A similar hyperplasia of elastica is to be noted in other previously elastic structures that have been subjected to increased strain, *e. g.*, the diseased heart valves of rheumatic and syphilitic heart disease and in the intimal coats of arteries. Pulmonary elastosis is really a common finding in patients with chronic rheumatic heart disease occurring in connection with pul-

monary interstitial fibrosis and at the same time with pulmonary hypertension and hypertrophy of the right ventricle. We have been impressed with the apparent parallelism of these findings in many cases. Pulmonary elastosis is not pathognomonic of the chronic rheumatic pneumonopathy, however, since it is found to some degree with advanced pulmonary interstitial fibrosis regardless of the underlying pathologic change. Its development, therefore, has a mechanical rather than a purely etiologic significance. It is of interest, however, that a moderate degree of elastic tissue hyperplasia is already evident in the lung sections of a majority of young rheumatic fever patients. In these patients the mitral valvular lesion is comparatively slight, certainly not that of stenosis, a fact that suggests to us that the obstructive process that causes right heart strain begins early within the lung structure in rheumatic fever.

The toughening of the lung has always been attributed to pulmonary passive congestion. However, it is often demonstrable in young rheumatic patients who never had definite congestive heart failure, except possibly in the last few days of life. The "rubberoid" lung in rheumatic heart disease in the subchronic and chronic state is usually distinctive in its consistency from that of the lung in chronic congestive heart failure, *e. g.*, after myocardial infarction or other lesions leading to chronic left ventricular failure with recurring pulmonary edema. In the latter case, the lung is often merely boggy from passive congestion. Since low-grade pneumonitis of varied bacterial origin is apt to develop in the presence of passive congestion,[1] it is not surprising to encounter occasionally increased firmness of the lung where congestive heart failure irrespective of etiology is the fundamental factor. The chronic pulmonary congestion of syphilitic heart disease is not infrequently accompanied by a mild fibrosis which, however, may be partly of infectious origin. The surprising thing is that interstitial fibrosis incidental to heart failure *per se* is often so slight in the non-rheumatic cases. On the other hand, a varying degree of toughness is found in the large majority of cases of chronic rheumatic heart disease regardless of the extent of congestion, often irrespective of the severity of the associated valvular heart lesion. Incidentally, we have noted its absence or slight development in a smaller group of patients with even advanced mitral stenosis, a fact that indicates to us that valvular disease *per se* is not the main causative factor of pulmonary interstitial fibrosis.[5]

Passive Congestion and the "Dry Lungs" of Chronic Rheumatic Heart Disease. Pulmonary congestion in chronic rheumatic heart disease depends on many factors. Some of these gray toughened lungs are strikingly free of passive congestion, while many, of course, show it in marked degree with or without pulmonary edema due to

heart failure. Not uncommonly, late pulmonary congestion is the result of a combination of factors: a recurrence of rheumatic activity as indicated by the presence of pneumonitis and carditis and associated terminal heart failure. This is often seen in the final cardiac defeat of middle-aged rheumatic patients, who die shortly after a mild respiratory infection, usually beginning in the upper respiratory tract. The altered consistency of the lung parenchyma due to previous attacks of pneumonitis is usually easily demonstrable despite the terminal congestion.

Severe chronic passive congestion with paroxysmal pulmonary edema is not as common in rheumatic heart disease as in other types of cardiac disease. While terminal congestion and edema are usually present, the lungs at necropsy are often comparatively dry. In many instances small foci of acute congestion with moderate escape of edematous fluid are separated by wide areas of noncongested lung tissue. There is in our experience a small but definite number of cases where the lung structure was rather strikingly dry, although there may have been coëxisting hydrothorax, and congestive failure in the remaining viscera. There may be curiously enough a greater degree of hyperemia in the bronchial mucosa, due possibly to marked congestion in the bronchial veins and capillaries. It is commonly thought that, even in the absence of decompensation, the lungs are the site of constant passive hyperemia due to back pressure secondary to mitral stenosis. For example, this was the reason advanced by Peabody for the decreased vital capacity noted in individuals with compensated valvular heart disease.[11] We are convinced that this is not necessarily so; in the occasional case of more or less sudden death in patients known to have compensated mitral stenosis we have seen no evidence of this supposed blood stasis. It is even more puzzling to observe such findings where heart failure with congestion of the viscera has actually occurred. Tricuspid stenosis and obstruction of the inferior vena cava, factors known to cause a relative ischemia of the lungs, were not factors in our material. These dry lungs for which we have no adequate explanation were mentioned casually by Paul,[10] but, as far as we know, no other reference to them exists in the literature.

The Relationship of Pulmonary Arterial Lesions to Rheumatic Pneumonopathy. In this paper we have not attempted to discuss the vascular lesions of rheumatic pneumonopathy. It is well known that in late rheumatic heart disease with mitral stenosis, advanced arteriosclerosis of the pulmonary artery may be present, involving especially the smaller branches. The extent of this development varies and does not appear to be in constant relationship to the parenchymal damage (Fig. 7). Unquestionably such extreme involvement as is sometimes seen must play an important rôle in the development of right heart strain. It may possibly introduce the

factor of ischemia in the development of chronic pneumonitis. This arteriosclerosis has its origin in part in rheumatic arteritis. We have observed the early appearance of pulmonary arteritis in acute rheumatic fever; it is generally collateral with the parenchymal changes and in a few instances by reason of extensive and unusually severe involvement, is the predominant lung lesion. However, it is our opinion that arteritis and arteriosclerosis are of secondary importance in the development and evolution of rheumatic lung disease. This is based on our observation: 1, That in the large majority of cases the acute pneumonia or pneumonitis overshadows the collateral arteritis; 2, that the advanced arteriosclerotic lesion of the pulmonary artery seen often in association with mitral stenosis is uncommon in young rheumatic fever patients; 3, that interstitital pulmonary fibrosis in such young subjects is often already widespread and well advanced. These facts indicate that the pulmonary arteriosclerosis of rheumatic cardiopulmonary disease is a later development, and that despite its partial origin in inflammatory processes, it is largely subsequent to chronic pneumonitis and pulmonary hypertension. We hope to describe in detail the rheumatic pulmonary vascular lesions in a separate report, now in preparation.

Summary. 1. The characteristic pneumonopathy of acute rheumatic fever can be identified as the precursor of an equally characteristic pulmonary change seen often in chronic rheumatic heart disease.

2. An intervening subacute stage is featured, as is the late chronic stage, by impaired elasticity of the lung tissue.

3. Histologic studies indicate that this pulmonary lesion is a chronic interstitial pneumonitis, which like rheumatic myocarditis, is often accompanied by evidence of recurring inflammation.

4. One of its characteristic features is a hyperplasia of elastic tissue probably indicative of hypertensive strain in the fine pulmonary circulation.

5. This pulmonary change is not directly dependent on the presence of passive congestion or of mitral stenosis, since both of those factors may be absent or developed in variable degree. Passive congestion undoubtedly intensifies the interstitial fibrosis, but remains in our opinion a secondary factor.

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THE RÔLE OF MITRAL STENOSIS AND OF POST-RHEUMATIC PULMONARY FIBROSIS IN THE EVOLUTION OF CHRONIC RHEUMATIC HEART DISEASE.

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Chronic heart failure in rheumatic heart disease has been ascribed for years to the mechanical effects of mitral stenosis. It is generally accepted that mitral stenosis by retarding the onward flow of blood causes enlargement of the left auricle, later an increasing stasis in the pulmonary veins, creating thereby a state of chronic congestion, and hypertension in the pulmonary vascular circuit. The right ventricle undergoes hypertrophy and dilatation, and ultimately fails in its effort to overcome this pulmonary hypertension. This apparently is the pathogenesis of right heart failure with its congestive enlargement of the liver and peripheral venous stasis that is so characteristic of advanced rheumatic heart disease. In the majority of cases this would appear to be a satisfactory explanation. We have, however, in the last 5 years come to the conclusion that another factor aside from mitral stenosis itself is, at least in some patients, the major cause of right heart failure. This belief is based on a number of observations, which we wish to discuss in this report.

1. *The Normal Sized Left Auricle in Occasional Cases of Mitral Stenosis.* It has been thought by the profession at large, even by cardiologists and roentgenologists, that enlargement of the left auricle is an inevitable sequel to mitral stenosis and a measure of its severity. It is unquestionably the *usual* finding in patients who had long continued mitral obstruction. Nevertheless we have encountered in a series of 61 cases of mitral stenosis, 7 instances in which the left auricle was not enlarged (Fig. 1). While the entire group included varying grades of stenosis 4 of the 7 examples of non-enlargement of the auricle occurred in the presence of advanced stenosis of the type that is often described as "pure" mitral stenosis. The lesions were characteristically rheumatic. There was slight to moderate enlargement of the auricular appendage in some of these 7 cases, certainly not marked in any and not comparable with the enlargement of the right auricular appendage in the same hearts. In no instance was there associated congenital heart disease. A larger group was noted to have a comparatively slight degree of left auricular enlargement. This is probably within common experience, but is also challenging in view of the fact that mitral stenosis, usually advanced in these cases, is a development of many years' duration.

In the normal adult heart the length of the unopened left auricle

measured externally is practically one-half that of the left ventricle, the ratio of auriculo-ventricular length being 50 to 55%. In mitral stenosis, the length of the left auricle is usually two-thirds to three-fourths of the length of the ventricle and occasionally may equal it. All of the 7 cases herein stated to have normal sized left auricles accompanying mitral stenosis were within the normal ratio of auriculo-ventricular length. The age of these patients varied from 17 to 64.

It appears then that valvular obstruction is not the sole factor in the progressive left auricular dilatation of rheumatic heart disease. Unquestionably other factors, anatomic and physiologic, exert a marked local influence on the auricular structure. They cannot be discussed here, but we have concluded that mitral valve obstruction is only one of a number of such factors, that its importance in initiating the train of events leading to right heart failure has probably been exaggerated, certainly so in types of cases of mitral stenosis just described.

2. *The Significance of Right Ventricular Involvement in Rheumatic Heart Disease and Its Relationship to Mitral Stenosis.* It has been a matter of interest to us, as well as to others, that some people with mitral stenosis live considerably longer than the usual patient with rheumatic heart disease. The patients who reach the age of 45 constitute a larger group than is generally realized. Interesting statistical data has been recorded in previous papers.[2,4,6,7,10]

We have observed that some patients with advanced mitral stenosis reached the 6th or 7th decade of life and at necrospy presented little or no evidence of congestive heart failure. This was in marked contrast with the large number of patients between the ages of 20 and 50 who having the same degree of mitral stenosis, presented the common evidence of right heart failure with congestive enlargement of the liver and peripheral venous stasis. The very different course in these two groups leads us to believe that mitral stenosis *per se* is not the factor that determines the outcome. The nature of a protective mechanism, if such actually exists, has been discussed by Levine and Fulton,[7] who suggested that systemic hypertension prolonged life in mitral stenosis by producing dilatation of the obstructed mitral ring. The one pathologic change in the heart aside from mitral stenosis that is commonly present in the early development of chronic right sided insufficiency is the combination of hypertrophy and dilatation of the right ventricle, especially of the outlet portion (conus), which we believe to signify prolonged strain. It is our observation that this change is often absent, and when present, usually in mild degree in those cases of advanced mitral stenosis, who reach a normal life expectancy. We believe therefore that the chief factor which, barring complications, determines the severity of the course and the duration of life is the degree of right ventricular strain and not the degree of mitral stenosis.

An analysis of 30 cases of mitral stenosis, chosen at random, illustrated in a general way the clinico-pathologic importance of right ventricular hypertrophy and dilatation. The patients varied in age from 22 to 67. They could be generally divided into two groups on the basis of right ventricular strain as evidenced by the structural changes in that ventricle. The larger group consisting of 20 patients, average age 42.3 years, had chronic right heart failure and all of them showed moderate to marked hypertrophy and dilatation of the right ventricle (Fig. 2). The smaller group consisting of 10 cases with normal or practically normal ventricle (Fig. 3), did not have chronic right heart failure; their average age at death was 51 years; death was attributed to non-cardiac disease (5 cases), to left heart failure following coronary thrombosis (1), or following obstruction by ball-valve thrombus in the left auricle (1), to embolism secondary to auricular fibrillation (3).

Right ventricular hypertrophy, eventually strain and failure is the accepted rule in mitral stenosis. It is evident, however, that some patients may have severe mitral stenosis that is not necessarily followed by right ventricular strain for many years. Moreover, there appears to be a fairly proportionate relationship between longevity or an approach to it in mitral stenosis and the degree of freedom from right ventricular strain. The latter is a response to some form of pulmonary resistance, which evidently may or may not develop in the presence of mitral stenosis. The importance of this pulmonary factor is emphasized in the following chapter.

3. *The Existence of Chronic Right Heart Failure in Rheumatism Without Mitral Stenosis.* We have noted 3 instances of aortic stenosis unaccompanied by mitral stenosis, in which the clinical picture was essentially the same as that usually ascribed to the latter lesion alone, namely chronic right heart failure (Figs. 6 and 7). In all 3 instances, the valvular lesion was undoubtedly rheumatic; the age of these patients was 35, 36, and 51 years. Isolated aortic stenosis in a young or middle aged patient is uncommon from the anatomic standpoint; accompanied by the development of chronic right heart failure, it is distinctly uncommon, but the existence of such cases is of great significance in the attempt to trace the evolution of rheumatic heart disease. It becomes more evident that the cause of right heart failure in chronic rheumatic heart disease is more directly related to an impediment in the pulmonary circulation. This factor was present in each of these 3 cases; hypertrophy and dilatation of the right ventricle were associated with early pulmonary atherosclerosis and an altered consistency in the lung structure which obviously was the basis of increased intrapulmonary resistance and pulmonary hypertension in the entire absence of mitral stenosis and resultant back pressure.

4. *The Lesions of the Pulmonary Vessels. The Relative Immunity of the Pulmonary Veins in Mitral Stenosis Accompanied by Pre-*

dominant Right Heart Failure. In the chronic stage of rheumatic heart disease, pulmonary arterial involvement is often conspicuous, more so than in the early acute phases of rheumatic fever, and differing from the acute arteritis of the early involvement in that it consists largely of atherosclerosis, which is a degenerative reaction (Fig. 8). This development can be reasonably associated with the presence of a pulmonary hypertension, as pointed out by Moschcowitz,[8a] Parker and Weiss.[9] The extent of the arterial degeneration is largely parallel on one hand with the degree of right ventricular hypertrophy and strain and on the other with the extent of a diffuse fibrosis in the lungs. We have just noted that pulmonary atherosclerosis and increased firmness of the lung structure were present in some cases of rheumatic heart disease in the absence of mitral stenosis (or any significant mitral valve lesion). It is also interesting that in patients with mitral stenosis, who reach middle or upper age with little or no cardiac disability, pulmonary atherosclerosis is usually slight (Fig. 5).

An interesting contrast to the state of the pulmonary artery and its branches in chronic rheumatic heart disease is afforded by the pulmonary veins. The relatively few observations concerning them are conflicting. Zinsser[11] found little involvement in the pulmonary veins in mitral stenosis. Brenner[3] found sclerosis constantly in some degree in the small pulmonary veins, less so in the large veins.

LEGENDS FOR FIGS. 1 TO 9.

FIG. 1.—*A*, Normal sized left auricle with advanced mitral stenosis; the right auricle is moderately enlarged. *B*, Markedly enlarged left auricle, with advanced mitral stenosis. The degree of valvular obstruction was practically identical in heart, Fig. 1, *A*. Both hearts viewed from the rear.

FIG. 2.—Extreme cor pulmonale in rheumatic heart disease with mitral stenosis, viewed from left lateral aspect; severe chronic right heart failure in association with advanced interstitial pulmonary fibrosis and acute pulmonary arteritis. Right ventricular wall (*R*) measured 15 mm.; pulmonary artery (*P.A.*).

FIG. 3.—Absence of right heart hypertrophy and dilatation in a case of advanced mitral stenosis (see Figs. 4 and 5); patient aged 52, well until 6 weeks before death from auricular fibrillation and pulmonary embolism. Right ventricular wall (*R*) measured 4 mm.

FIG. 4.—Advanced mitral stenosis without right ventricular hypertrophy (see Fig. 3).

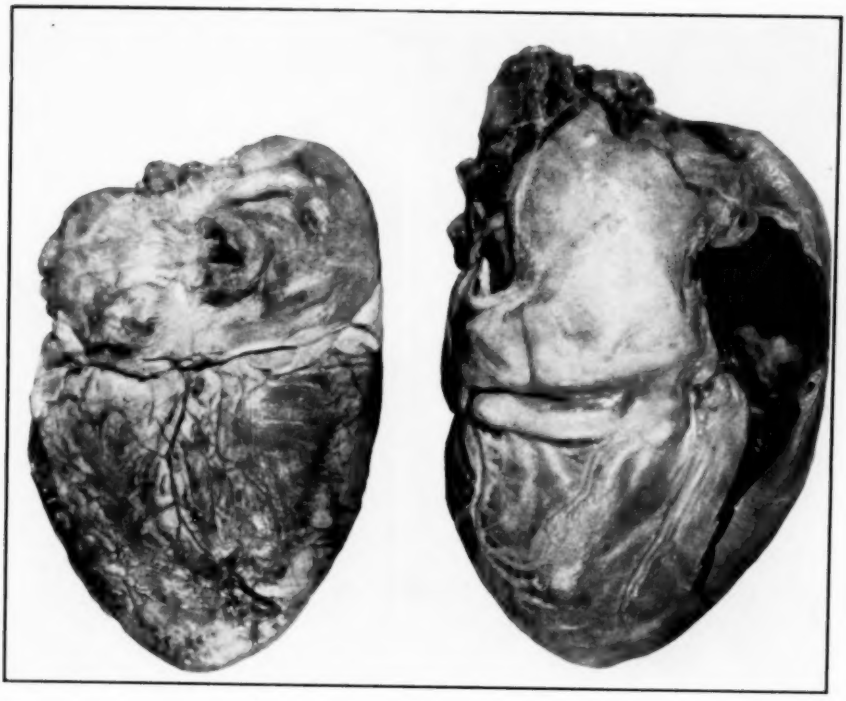
FIG. 5.—Absence of pulmonary arteriosclerosis in a case of advanced mitral stenosis (see Figs. 3 and 4). No significant sclerosis noted in small branches. The right ventricle was normal.

FIG. 6.—Hypertrophy and dilatation of right ventricle in a man, aged 36, with advanced post-rheumatic aortic stenosis and practically normal mitral valve (see Fig. 7). Death by chronic right heart failure. Right ventricular wall (*R*) measured 7 cm.

FIG. 7.—Slightly scarred but functionally normal mitral valve (see Fig. 6).

FIG. 8.—Marked pulmonary arteriosclerosis in association with mitral stenosis and chronic right heart failure.

FIG. 9.—Normal pulmonary veins in association with mitral stenosis and chronic right heart failure (see Fig. 8). The translucency of the normal pulmonary veins is lost in the photography.



A B

FIG. 1

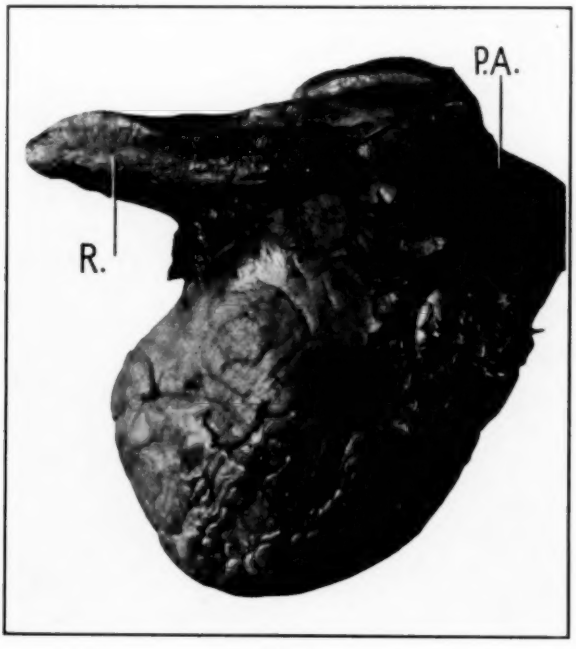


FIG. 2

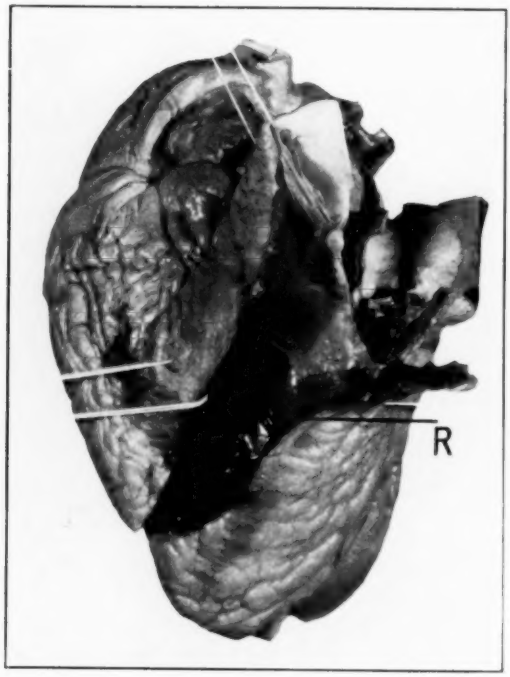


FIG. 3

FIG. 4

FIG. 5

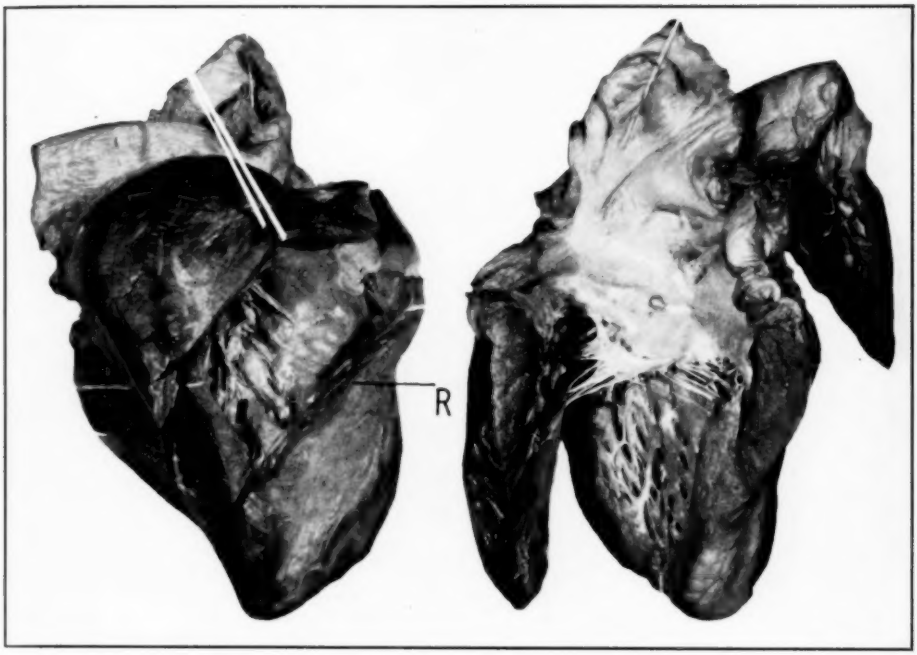


FIG. 6 FIG. 7

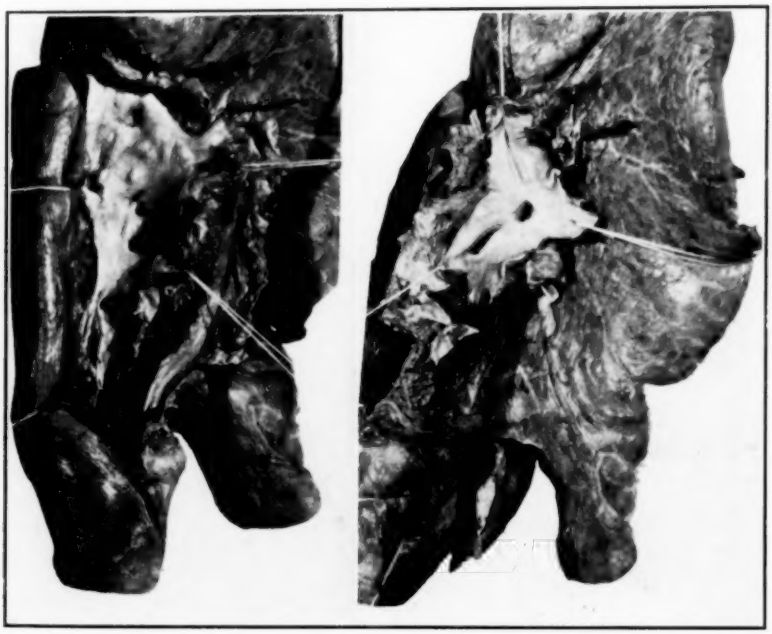


FIG. 8 FIG. 9

Indeed he found these changes in almost all lungs, in patients above the age of 10, regardless of the presence or absence of cardio-pulmonary disease. Some investigators found pulmonary phlebosclerosis in mitral stenosis increased with heart failure, but no reference has been made as far as we know as to the predominant type of failure in such patients: which is important because we have consistently found evidence of significant pulmonary phlebosclerosis in those patients who have suffered from predominant chronic left heart failure or at least a generalized type of failure regardless of etiologic considerations. Contrariwise, a fairly consistent necropsy observation is the relative immunity of the larger pulmonary veins in uncomplicated mitral stenosis with chronic right heart failure (Fig. 9). In such cases the contrasting pulmonary artery disease is often marked. In most of them some thickening of the venules usually slight to moderate was seen, similar to that noted by Brenner in practically all individuals, but there was a significant diminution of phlebosclerosis as one successively examined small, medium, and finally large sized branches of the pulmonary veins. This immunity was not so apparent with complicating left heart failure or when there was unusually marked left auricular enlargement and resulting dilatation of the orifices of the pulmonary veins. In such cases the existence of back stasis in the pulmonary veins was suggested by phlebosclerosis in large vessels which sometimes equalled that seen in patients with repeated myocardial infarction, decompensated hypertensive cardio-renal disease and other types of chronic left heart failure. Its slight development in uncomplicated mitral stenosis with ordinary auricular enlargement and predominant right heart strain strikes in our opinion at the theory of retrograde pulmonary venous hypertension originating at the mitral valve. The continuous obstruction of many years' duration usually associated with mitral stenosis ought to be productive of a pulmonary phlebosclerosis more intensive than seen with any other type of heart disease.

The Rôle of Chronic Pneumonitis in the Evolution of Rheumatic Heart Disease. The immediate cause of the pulmonary hypertension is, we believe, a diffuse interstitial lung fibrosis. Anoxemic fibrosis (brown induration of the lung) secondary to heart failure and congestive stasis has long been known to pathologists, and it has always been assumed that the pulmonary changes in rheumatic heart disease were entirely of that type, and basically the result of obstruction at the mitral valve. The importance of pulmonary fibrosis in conjunction with pulmonary hypertension and mitral stenosis has been recognized. Moschcowitz (1930)[88] attributed the process, as others previously, to secondary capillary stasis and in the late stages to ischemia following advanced pulmonary arteriosclerosis. He employed the term "arterio-capillary fibrosis" (Gull and Sutton) and showed a similarity of the pulmonary and renal

capillary lesions in their association with hypertension. Parker and Weiss[9] in the latest work on this subject also emphasized the fibrotic changes in the capillary vessels and alveolar walls and their effect on gaseous exchange, but they likewise considered these lung changes to be a secondary result of chronic left heart failure ("back pressure"). In their case of mitral stenosis they thought that right heart involvement was a terminal event due to a malignant pulmonary hypertension which had developed rapidly toward the end of life.

The observations herein recorded make it difficult for us to apply the theory of back pressure and stasis to all cases of mitral stenosis without reservation. There is reason to believe that in some patients (and possibly this in time will be found applicable to others) the essential cause of the failure is not in valvular obstruction but rather in an important and independent structural change in the lung. This phenomenon is in the beginning a direct result of rheumatic fever, a pneumonitis leading often to a widespread fine interstitial fibrosis, which may with recurrences of the inflammatory reaction become progressively severe. The transition from the acute rheumatic lung lesions to the later stages of post-inflammatory fibrosis has been recently reported.[5b] The development of pneumonitis in rheumatic fever is concurrent with cardiac involvement; nevertheless, we have seen instances especially in children, where the almost inevitable mitral valvular lesion was comparatively slight, far from actual stenosis and yet at the same time pneumonitis had already developed into the "rubberoid" lung. In these early victims of rheumatic disease the obstructive pulmonary factor was already evident, in the early hypertrophy and marked dilatation of the right ventricle. It may be pointed out that chronic congestive heart failure of the type associated with paroxysmal dyspnea, and recurring pulmonary edema is seldom present in such young patients.

The writer has observed the presence of cardiac murmurs in the pulmonary area in children after an attack of rheumatic fever in whom no murmurs were previously heard. A short but sometimes rough systolic murmur followed by marked accentuation of P-2 are not infrequent under such circumstances; such murmurs in the area of "auscultatory romance" are difficult to assess. The fact that the development of mitral stenosis occurs at least a few years after the early attacks of rheumatic fever[1] leads us to believe that some of these murmurs in the pulmonic area may be related to increased pulmonary tension.

In the later stages of chronic rheumatic heart disease the development of left venticular failure in numerous patients adds to the pulmonary obstruction by the imposition of passive congestion on a vascular circuit already handicapped by post-inflammatory interstitial fibrosis. In this connection the extent of the valvular ob-

struction is apparently of little importance as long as the integrity of the left ventricle is maintained. A normal or well functioning left ventricle gives the right ventricle opportunity to meet whatever obstruction exists in the pulmonary capillary bed that has resulted from the original inflammatory process. A constant passive congestion of the lungs has been assumed to exist in all patients with mitral stenosis. That this may be a fallacy was discussed by us in a previous paper,[5] in which attention was called to the interesting and not infrequent necropsy finding of the "dry lungs" in chronic rheumatic heart disease. Those patients who are ambulatory and completely compensated and with characteristically normal or even small left ventricle show no Roentgen or clinical evidence of passive congestion of the lungs.

The heart in rheumatic disease cannot be considered alone in reference to circulatory efficiency. The pulmonary status assumes in our opinion equal importance. The extent of the intrapulmonary blockade and the ability of the right ventricle to cope with it determines the course and prognosis of each case. The importance of recurring myocarditis is recognized; in our opinion, it hastens but scarcely alters the general pattern of cardiac failure in adult patients. The same may be said of auricular fibrillation, unless fatal embolism supervenes. The situation is aggravated of course if and when the left ventricle fails. Aside from recurring inflammation, there are structural changes in many rheumatic hearts that lead to the complication of left ventricular strain and ultimately generalized failure (serious aortic valvular disease, adherent pericardium, the hypertrophy and strain of essential systemic hypertension). In their absence, left ventricular failure is usually a subterminal event coming on many years after the development of right ventricular strain.

It is true that the majority of patients with rheumatic heart disease have no history of acute pulmonary involvement at any time. It was pointed out, however, that in many instances a subtle subclinical pneumonitis had occurred and was discovered only at necropsy.[5a] The mitral valvular lesion and the interstitial pulmonary fibrosis are not in a given case parallel in extent with each other. It is very likely that in many patients a comparatively mild pulmonary lesion disappears in early life while the mitral valvulitis persists and progresses in the later years. Thus patients are occasionally seen with advanced mitral obstruction, even beyond middle age, in whom the parenchymal lung lesion is slight.

Summary. We have discussed the probability: 1, that mitral stenosis in some patients is in itself not the sole or possibly even an important factor in the causation of the chronic right heart failure which characteristically terminates chronic rheumatic heart disease; 2, such failure may occur even in the absence of significant mitral valvular dysfunction; 3, the key lesion in this particular

type of patient is the association of an intrapulmonary lesion with right ventricular strain; 4, the intrapulmonary lesion is a diffuse fibrosis that at least in its beginning is a direct result of rheumatic pneumonitis; 5, the factor of passive pulmonary congestion becomes important with the development of left ventricular failure which may or may not occur.

The protocols of the cases of mitral stenosis with normal sized left auricle and also of those concerned with the structural changes in the right ventricle have been omitted. They are listed separately and are available on application to the author.

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THE SITE OF ACTION OF THE RENAL PRESSOR SUBSTANCE.*

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The experiments to be reported were undertaken in order to investigate the mechanism of action of the renal pressor substance (Tigerstedt's "renin").

Method. The observations were made on heparinized rats which were anesthetized with sodium pentobarbital. The pressor substance was prepared by treating ground renal cortex with alcohol and extracting the precipitate with water as described by Merrill, Williams and Harrison.[3] Various structures were removed, destroyed or separated from the circulatory systems of the test animals, and the active material was then injected through an aortic cannula. The cannula was equipped with a side connection through which blood pressure was measured with a mercury manometer. The rises in blood pressure due to the volume of fluid injected were determined by administering equal volumes of 0.9% sodium chloride solution. In the first series of experiments no attempt was made to determine whether these procedures altered the degree of pressor response but simply whether they abolished it.

* This investigation was aided by a grant from the Josiah Macy, Jr., Foundation.

The Influence of the Nervous System. In one group of experiments a tracheal cannula was inserted, artificial respiration was administered, and the connections between the brain and the remainder of the body were destroyed by clamping all the cervical structures except the trachea in the lower part of the neck. The clamp crushed the cord, the vagus nerves and the blood-vessels. Each of 7 rats so treated exhibited markedly greater response to "renin" than to saline. The response of these animals was usually greater than that observed in rats with intact cords, the difference probably being due to the low initial pressure which followed destruction of the spinal cord. In a second series of experiments, the spinal cord was exposed in the neck and the lower portions of it were destroyed by passing a wire down the vertebral canal, artificial respiration being maintained through the tracheal cannula. Each of 5 rats so treated displayed a well-marked pressor response to renin.

These observations are in agreement with those of previous workers[1,4] in showing that the rise in blood pressure produced by the renal pressor substance is independent of central nervous system influences. The results do not, however, demonstrate a direct peripheral vasoconstrictor action of this substance, for it is conceivable that the effect might be due to some substance formed in other parts of the body and liberated by the injection of renal extract. In order to study this question further experiments were done.

Effect of Removal of Various Organs From the Circulation. The possibility that the pressor effects of renin could be due to substances formed in the hypophysis was excluded by the experiments already mentioned, in which the structures in the lower part of the neck were tightly occluded by a clamp. Since under these conditions the venous return from the hypophysis was blocked it is clear that secretions from these organs could not have been responsible for the pressor effect.

In order to study the possible rôle of the lungs comparisons were made of the effect of intravenous and intra-aortic injections. It was found that the initial depressor effect produced by renal extract was usually more pronounced when the intravenous route was employed. This result was interpreted as meaning that our extracts probably contained peptones, which have been shown by Mauntner and Pick[2] to cause constriction of the pulmonary vessels. (The method of preparation of the extracts makes it unlikely that they could contain histamine, which may have a similar action on the pulmonary vessels.) When allowance was made for the greater depressor effect no significant difference was found between the effects of intra-aortic and intravenous administration.

The liver was excluded from the circulation by diverting the portal blood into one of the renal veins with a curved cannula, the

hepatic artery being ligated. Only two successful preparations were obtained. Both of these rats showed a well-marked pressor response to renal extract, the effects being greater—probably because of the lower initial blood pressure—than those obtained on control animals with intact livers.

Removal of the spleen—1 rat—and of the pancreas—5 rats—did not abolish the pressor effect which was about the same as that obtained on untreated animals.

In 6 rats the adrenal glands were removed immediately before the injection. All of these animals showed normal responses when renin was administered.

In 10 experiments the renal pedicles were alternately clamped and released during injections of renal extract. Removing the kidneys from the circulation did not alter the pressor effects.

These observations suggest that the rise in blood pressure produced by renin is due to a direct local effect on the vessels. The question was studied further by observing the effect of the extract administered locally on the perfusion rate through the leg. In some experiments, a cannula pointing toward the head was inserted into the proximal part of the left common iliac artery, the aorta being clamped just above its bifurcation during the measurements of the perfusion rate and released between such measurements so that the blood supply was maintained to the right leg except during the time when the rate of flow through the right common iliac artery was being determined. In other experiments, a cannula pointing toward the foot was placed into the femoral artery of the excised leg, separated completely from the body. The results obtained with both types of experiment were similar and are illustrated in Figure 1. The administration of renin was followed by well-marked vasoconstriction in the vessels of the leg, although the duration of the effect—5 to 10 minutes—was usually considerably less than the usual duration—15 to 30 minutes—of the pressor response in intact animals. Whether this difference is to be ascribed to the fact that the pressor substance was rapidly washed out of the leg by the perfusion fluid or to some other reason is uncertain, but the experiments do indicate clearly that renin causes local vascular contraction, independently of the nervous system, and that the pressor effect is a direct one in the sense that it is not due to the liberation of pressor substances from other parts of the body but is dependent on the effect of renin itself on the blood-vessels.

The experiments which were mentioned above in which it was shown that clamping the renal pedicles did not alter the response of the animals to renal extract seem, at first sight, to be contrary to those of Tigerstedt and Bergman,[4] who found that bilateral nephrectomy caused rabbits to become more sensitive to renin. They attributed this to the inability of such animals to excrete

renin. In order to investigate the reason for the difference between their results and ours, further experiments were done, the kidneys being removed from a series of rats, which were compared 2 or 3 days later with control animals as regards sensitivity. These experiments (Fig. 2) indicated clearly that rats which have had their kidneys removed 2 or 3 days previously are more sensitive to renal extract than are normal animals. On the other hand, it was found that nephrectomy or clamping the renal pedicles immediately before the injection did not increase the sensitivity of the animals (Fig. 2). The results confirm the findings of Tigerstedt and Bergman, but do not support their assumption that the difference in sensitivity is due to failure of the nephrectomized animals to excrete the pressor substance. The reason for the increased sensitivity of the latter rats is not clear at the present time and needs to be studied further.

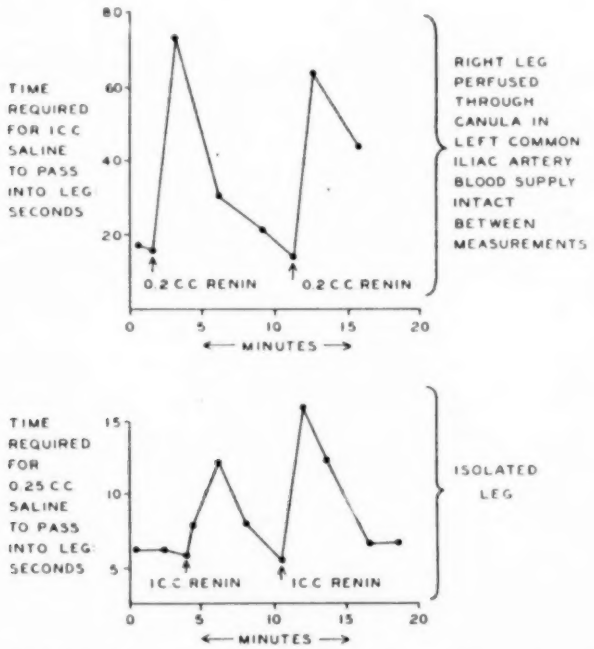

FIG. 1.—The two experiments illustrate the local vasoconstrictor action of renin as shown by a decrease in the perfusion rate through the leg.

The experiments indicate that the renal pressor substance has a direct vasoconstrictor action, which occurs independently of structures other than the blood-vessels. The pressor response is not abolished immediately after removal of various structures. However, removal of the kidneys does modify the action of the pressor substance provided that the animal has been deprived of the renal

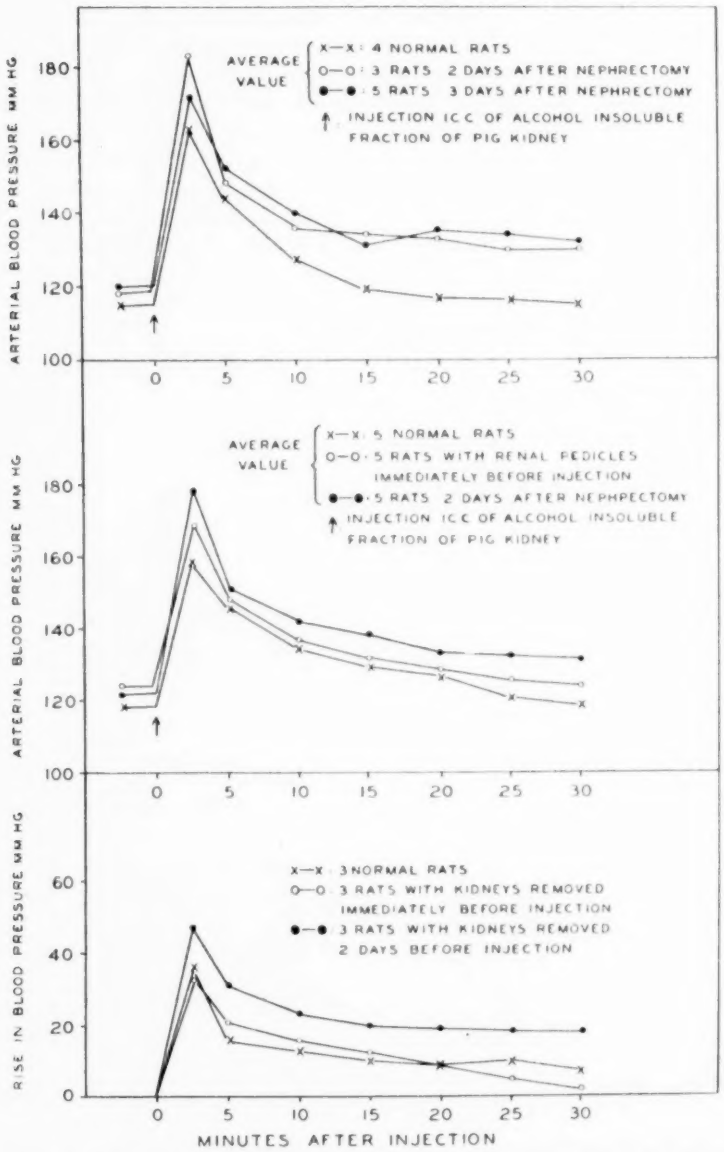
ARTERIAL BLOOD PRESSURE MM HG
AVERAGE VALUE
X—X: 4 NORMAL RATS
O—O: 3 RATS 2 DAYS AFTER NEPHRECTOMY
●—●: 5 RATS 3 DAYS AFTER NEPHRECTOMY
INJECTION 1C.C OF ALCOHOL INSOLUBLE FRACTION OF PIG KIDNEY
ARTERIAL BLOOD PRESSURE MM HG
AVERAGE VALUE
X—X: 5 NORMAL RATS
O—O: 5 RATS WITH RENAL PEDICLES IMMEDIATELY BEFORE INJECTION
●—●: 5 RATS 2 DAYS AFTER NEPHPECTOMY
INJECTION 1C.C OF ALCOHOL INSOLUBLE FRACTION OF PIG KIDNEY
RISE IN BLOOD PRESSURE MM HG
X—X: 3 NORMAL RATS
O—O: 3 RATS WITH KIDNEYS REMOVED IMMEDIATELY BEFORE INJECTION
●—●: 3 RATS WITH KIDNEYS REMOVED 2 DAYS BEFORE INJECTION
MINUTES AFTER INJECTION

FIG. 2.—Two or 3 days after bilateral nephrectomy the sensitivity of the animals to renin was markedly increased, particularly as regards the duration of the effect (*A*, *B*, *C*). Ligation of the renal pedicles immediately before the injection of renal extract had practically no effect on the response to renin (*B*). Likewise the response was not altered immediately after removal of the kidneys (*C*).

tissue for a sufficiently long period. It seems quite possible that several days after the removal of other organs the effect might also be modified even though the response is not changed immediately after the exclusion of these structures. Experiments aimed at testing this hypothesis are now in progress.

Summary. Injection of the renal pressor substance—renin—caused rise in blood pressure after destruction of the spinal cord, and after exclusion of the hypophysis, adrenals, pancreas, liver and kidneys from the circulation. A vasoconstrictor effect of this substance was demonstrated in the isolated leg. Although the character of the pressor response was not altered by removing the kidneys immediately before the injection, it was found that the height and duration of the rise in blood pressure were increased in animals which had been subjected to nephrectomy 2 or 3 days previously.

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THE INSENSIBLE LOSS OF WATER IN DIABETES INSIPIDUS.*

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Scant attention has been paid to the measurement of the insensible loss of water in diabetes insipidus in spite of the fact that this loss forms an important item in the total water balance. Early studies were published by Strubell[9] and Veil;[10a,b] but their technique was inaccurate and their results discordant. In normal subjects, the insensible loss of water is a function of the total metabolism[8] and appears to be independent of the less extreme dislocations of the water exchange. Water diuresis, and antidiuresis produced by the injection of pituitrin, are usually found to have no influence on the insensible weight loss,[1,2,3] although Manchester and co-workers[6] reported an altered loss under these conditions. In patients with diabetes insipidus it is possible to extend these observations, as one can cause rapid and large shifts in the intake and output of water by the administration and withdrawal of pituitrin. Lavietes[4] recently reported that the insensible loss of weight of such a patient

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varied from 840 to 1644 gm. a day over a period of 9 days, during which the volume and osmotic pressure of the body fluids were varied greatly by the use of pituitrin and by changes in the salt intake. He observed no correlation between the variations in the insensible loss and the changes produced in the body hydration.

Furthermore, to understand the disturbed physiology of diabetes insipidus it is important to know whether or not the insensible loss of water differs essentially from that found in normal individuals. Such a difference would suggest that the metabolic anomaly in that disease is more widespread than one having to do solely with the control of the urine volume by the kidneys.

Clinical Abstracts.* SUBJECT K. was a 31-year-old housewife of Hungarian extraction who complained of amenorrhea, polyuria, and an increase of 25 pounds in weight, all within the few months previous to the observations recorded in this paper. The routine physical examination was negative, as were the neurologic examination, visual fields, serologic tests, spinal fluid findings, and the Roentgen ray of the region of the *sella turcica*. Except for the low specific gravity, routine examination of the urine was negative.

SUBJECT L., a 21-year-old, unmarried girl, evidently had a congenital type of diabetes insipidus. Her polyuria and polydipsia started early in life, and her mother had suffered from similar symptoms. Routine physical and neurologic examinations were negative, as were her visual fields, serologic tests and Roentgen ray of the *sella turcica*. Her urine usually contained a faint trace of albumin, too little to quantitate accurately; the urinary sediment was negative.

Methods. The insensible loss of water of each subject was determined for a number of consecutive days while the diabetes insipidus was alternately controlled with pituitrin and allowed to go unchecked. Pituitrin was driven intramuscularly in doses of 0.5 cc. of the obstetrical preparation on the days designated by a P in the date column of the tables. In determining the insensible loss of water the technique of Newburgh, as described in his several papers,[5] was carefully followed. The chair balance used to weigh both subject and urine specimens had a sensitivity of 1 to 5 gm., depending on the load; the food consumed and the stools were weighed on a smaller balance to the nearest gram. The subjects were hospitalized and instructed to establish as nearly as possible a constant plane of activity, to avoid sensible perspiration or undue cooling, and to refrain from bathing. The term $(CO_2—O_2)$ which is subtracted from the insensible loss of weight to obtain the insensible water loss (Table 1) was calculated as described by Newburgh.[5] No allowance was made for the heat expended in warming to body temperature the large volume of water the subjects drank, as it was found that on an extreme day, March 25, when Subject L. consumed over 10 liters of water, such a correction would have changed the term $(CO_2—O_2)$ by only 4 gm.

Insensible Loss of Water. In Table 1, Column 4 gives the values for the daily insensible water loss, while Column 5 shows the effect of the pituitrin injections on the urine volume.

In the case of Subject K., the polyuria and polydipsia which

* We are indebted to Dr. Allan T. Kenyon for the opportunity to study both these cases.

accompanied the withdrawal of pituitrin was associated on 3 out of 4 days with a somewhat decreased insensible loss of water. From Table 2 it will be seen that on 2 of these days, December 13 and December 17, a strongly negative water balance occurred, while the third day, December 18, marked the recovery from an especially severe dehydration. As Subject K. weighed 80 kg., a loss of 3 liters would represent a loss of 5% of her total body water (calculating the latter as 70% of her body weight). It is possible that such a marked dehydration may cause a decrease in the insensible loss of water. Manchester, Husted and McQuarrie[6] reported that the insensible weight loss decreased in a manner parallel to the dehydration they produced in epileptic children; but Levine and Wyatt[5] failed to observe such a correlation. Newburgh and Johnston[7] and Hall and McClure[2] agree that a dehydration in which less than 6% of the total body water is lost has no effect on the insensible loss of water of normal subjects, while in the experiments of Hall and McClure a more severe dehydration was associated with a decreased insensible loss.

TABLE 1.—THE INSENSIBLE LOSS OF WATER IN DIABETES INSIPIDUS.

Date. (1)	Insensible weight loss. (2)	CO_2-O_2 (3)	Insensible water. (4)	Urine. (5)
	Subject K.			
12/11 P*	870	82	788	4,055
12 P	832	82	750	3,322
13	705	82	623	8,180
14	811	82	734	5,117
15 P	859	82	777	3,001
16 P	827	82	745	3,022
17	630	82	548	10,265
18	702	82	620	6,692
	Subject L.			
3/18 P	1247	71	1176	2,600
19 P	1212	71	1141	1,408
20 P	1156	97	1059	4,558
21 P	1209	97	1112	3,008
22	1097	99	998	7,180
23	1135	99	1036	8,911
24	1092	99	993	9,884
25	1054	99	955	10,520
26 P	1109	99	1010	3,935

* P in Column 1 indicates that pituitrin was given that day.

We are not at all sure that dehydration accounts for the decrease in K.'s insensible water on the days in question. She felt very badly when pituitrin was withdrawn and may, as a result, have been less active, just as was the normal subject of Newburgh and Johnston when he was undergoing dehydration. Also, the change

in the insensible water is small enough in magnitude to make it difficult to be sure of its significance. Thus from Newburgh's most recent work,[8] in which the energy output calculated from the insensible loss of water is compared with that observed by simultaneous indirect calorimetry in the respiration chamber, it is clear that in an individual 24-hour period the insensible water loss may not show quite its usual relationship to the total expenditure of energy.

We believe that a reduced total metabolism resulting from a decrease in activity accounts for the fact that Subject L.'s insensible losses were uniformly about 10% lower during the second period of 4 days when pituitrin was withheld than they had been during the first 4 days of pituitrin administration. Subject L. had led a very active life and slowly accustomed herself to the hospital régime.

Withdrawal of pituitrin, which leaves the diabetes insipidus uncontrolled, has, then, at most, only a minor effect on the insensible water loss, which latter bears its usual close relationship to the total metabolism.

TABLE 2.—ESTIMATED WATER BALANCE IN 2 CASES OF DIABETES INSIPIDUS.

Date. (1)	Estimated. Intake. (2)	Output. (3)	Balance. (4)	Observed weight change. (5)
		Subject K.		
12/11 P	3,231	4,806	−1575	−1510
12 P	4,940	4,037	+ 903	+ 983
12/13	6,092	8,871	−2779	−2973
14	8,305	5,803	+2502	+2549
12/15 P	4,399	3,729	+ 670	+ 744
16 P	3,691	3,718	− 27	+ 102
12/17	7,624	11,423	−3799	−4075
18	7,779	7,311	+ 468	+ 463
		Subject L.		
3/18 P	4,751	3,844	+ 907	+ 794
19 P	3,547	2,555	+ 992	+ 882
20 P	4,612	5,641	−1029	−1066
21 P	4,748	4,168	+ 580	+ 532
3/22	7,473	8,157	− 684	− 708
23	10,542	9,970	+ 572	+ 563
24	11,082	10,949	+ 133	+ 138
25	11,729	11,539	+ 190	+ 210
3/26 P	5,169	4,984	+ 185	+ 203

Water Balance. The principal change observed in discontinuing the administration of pituitrin to a subject with diabetes insipidus is the marked increase in the water consumed and in the urine voided. These two items of the water balance, together with the insensible water, were carefully measured in our observations. The

other terms in the fluid exchange, namely, the amounts of water in the urine and stool, were not determined, but calculated indirectly, and the resulting estimated water balances are presented in Table 2. The water intake, Column 2, is the sum of the water drunk, plus the water content of the food derived from standard tables, plus the metabolic water calculated in the usual way from the metabolic mixture. The figures for the water output in Column 3 represent the sum of the insensible water plus the water excreted in the urine and stool (the last item estimated from the generalization that fresh stool contains about 80% water). It is well recognized that for short periods of time and when a maintenance diet is fed, changes in the body weight closely approximate the water balance. Thus the figures in Column 5 serve as a check on the estimated balance values in Column 4.

It will be noted that Subject K. showed a very unstable balance with a tendency to frequent dehydration while Subject L. was much less variable in her water exchange. She had had her diabetes insipidus all her life and never resisted her thirst whereas Subject K. had suffered only a few months, was extremely dissatisfied with her condition, and undoubtedly attempted to control her polyuria by drinking less.

Summary. We have determined the daily insensible loss of water in 2 cases of diabetes insipidus in which the water exchange was subjected to large fluctuations by the administration and withdrawal of pituitrin. The insensible water loss is of the same order of magnitude whether or not pituitrin is injected and evidently bears in diabetes insipidus its usual close relationship to the total metabolism. The variations observed in the insensible loss of water were considered to be due to changes in activity rather than to dislocations in the water exchange, although the changes were of small enough magnitude to make the distinction difficult with the methods available.

Estimated water balances were calculated from the metabolic data. One subject, K., showed a very labile balance with a tendency to dehydration, while L. was much more stable in regard to her water exchange.

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OBSERVATIONS ON THE CONTINUED USE OF PROTAMINE ZINC INSULIN IN PATIENTS WITH SEVERE DIABETES MELLITUS.

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Protamine insulin* in the treatment of diabetes mellitus was first reported in this country in January, 1936.[2,5] Although this method of therapy has now been in use for almost 2 years and there have been numerous published reports, there is little specific information, even in the more recent papers,[1,3,4,6,7] as to the number of cases treated, the duration of the diabetes, the previous soluble insulin requirement in units and doses, and whether it was necessary to continue soluble insulin in conjunction with the protamine. Furthermore, objective data on the effect of protamine insulin on the clinical condition of the patient, *i. e.*, weight changes, tendency to glycosuria or insulin shock, and so forth, are meager. It is understandable that in the earlier publications follow-up records were not possible; but even the more recent reports still give little data on the effect of the continued use of protamine zinc insulin. In the earlier reports of protamine insulin most of the attention was given to the level of the blood sugar in the patients treated. Blood sugar curves were done on patients with protamine insulin and it was obvious that this form of insulin had the ability to reduce the blood sugar for a more prolonged period than did soluble insulin.[5,7] It was our experience in observing the effects of protamine insulin on the blood sugar for 24 hours at 2-hour intervals that a somewhat more constant level of blood sugar was maintained than with soluble insulin, although considerable variations were still present. Very little attention was paid to the glycosuria, although this is probably a more accurate index of the status of the diabetic patient throughout the day.

We are reporting a group of 20 patients, 16 of whom have been studied for periods of not less than 8 months while receiving protamine zinc insulin. The other 4 were observed for 1 to 2 months

* The protamine zinc insulin used in this study was Protamine Zinc Insulin Lilly.

in the hospital, at the end of which time protamine insulin was discontinued owing to the fact that it was impossible to prevent a significant degree of glycosuria. All of the patients reported had previously been under our observation and treatment in the clinic for an equal or longer period of time on soluble insulin.

Observations. In this group of patients 12 were males and 8 were females. The ages varied from 9 to 70 years; 6 patients were between 9 and 16 years, 4 between 20 and 25, 5 between 30 and 40, 4 between 40 and 50 and 1 patient was 70 years of age. All of these patients had had diabetes mellitus for more than 2 years. The average duration of the disease was 6 years. The details of the patients are given in Table 1.

TABLE 1.—DATA ON 20 CASES STUDIED.

Case No.	Age in years.	Sex.	Duration of diabetes years.
1	40	F	14
2	50	F	7
3	38	M	2½
4	41	M	5
5	34	F	14
6	11	F	2
7	33	F	6
8	24	F	3
9	25	M	10
10	14	F	4
11	35	M	9
12	16	M	4
13	20	M	4
14	21	M	3
15	37	M	8
16	9	F	5
17	10	M	4½
18	70	M	13
19	12	M	6
20	52	M	4

The procedure used in studying these cases was as follows. Each patient was hospitalized and the soluble insulin requirement and diet as observed in the clinic were checked. When we were satisfied how much of the soluble insulin was required to prevent glycosuria, protamine zinc insulin was begun. During the first period of treatment with protamine the soluble insulin was gradually reduced and when possible was discontinued. Urines were collected for the entire 24 hours in 4 fractional periods; from after breakfast to before lunch, from after lunch to before supper, from after supper to 8 P.M. and from 8 P.M. to before breakfast, which was usually 8 A.M. Frequent blood sugars were taken during this period of adjustment and in several cases 24-hour blood sugar determinations were made every 2 hours during the initial period of adjustment. These 24-hour blood sugar determinations are not reported because our findings were similar to those of other observers.

Results. Table 1 gives the age, sex and duration of the diabetes in the patients studied. In Table 2 is summarized the soluble insulin prior to protamine therapy, the insulin both soluble and protamine during the early period of protamine therapy and the final insulin requirement, both soluble and protamine, at the end of the period reported. We have designated the time during which the patients responded fairly well to protamine insulin therapy as the "early period." As the average of this was 6 months, we have also reported in Table 2 the status at 6 months of the patients who continued to do well on protamine insulin for longer periods.

TABLE 2.—INSULIN REQUIREMENTS BEFORE AND DURING PROTAMINE INSULIN THERAPY.

Case No.	Daily units.	No. of doses daily.	Time observed in months.	Total daily protamine insulin.		Added daily regular insulin.		Time in months.	Total daily protamine insulin.		Added daily regular insulin.		Total duration protamine therapy in months.	Present status.
				Units.	No. of doses.	Units.	No. of doses.		Units.	No. of doses.	Units.	No. of doses.		
1	145	4	62	95	2	35	2	7	120	2	20	1	16	Discontinued
2	80	4	49	32	2	0	0	3	40	2	0	0	16	Same
3	85	4	5	37	2	14	1	11	30	1	30	2	17	Same
4	60	4	5	72	2	0	0	8	20	2	60	2	16	Same
5	85	4	45	45	1	10	1	6	45	1	10	1	13	Same
6	45	3	15	25	1	10	1	7	10	1	55	2	10	Discontinued
7	50	3	37	25	1	10	1	6	25	1	10	1	10	Same
8	75	4	36	45	2	25	2	7	30	1	30	2	10	Discontinued
9	75	3	4	40	2	15	2	3	20	1	25	2	8	Same
10	60	3	28	50	2	10	1	8	25	1	25	2	14	Same
11	50	3	45	60	2	0	0	9	60	2	12	1	15	Same
12	100	4	31	40	2	30	2	8	30	2	0	0	23	Same
13	65	4	24	30	2	0	0	7	40	2	0	0	14	Same
14	110	4	36	45	2	35	2	6	90	2	38	3	19	Same
15	65	4	72	53	2	0	0	6	50	2	5	1	13	Discontinued
16	65	4	60	30	2	15	2	3	40	2	30	3	8	Discontinued
17	40	4	36	25	1	10	1	2	25	1	15	1	2	Discontinued
18	65	4	48	30	1	20	1	2	30	2	45	2	2	Discontinued
19	40	3	3	40	2	0	0	1	25	1	0	0	1	Discontinued
20	85	4	53	70	2	20	1	1	75	2	20	1	1	Discontinued

Of the 20 patients treated, 4 were never successfully transferred to protamine insulin (Cases 17, 18, 19, 20) and the attempt was discontinued at the end of 1 or 2 months. These 4 patients were hospitalized during this entire period of observation and various arrangements in the amounts of protamine insulin, the time of its administration, as well as combinations with soluble insulin, were tried without success.

In the remaining 16 patients protamine insulin was used for periods varying from 8 to 23 months. In 5 of these (Cases 1, 6, 8,

15, 16) it was necessary to discontinue the protamine insulin because it became impossible to control the glycosuria without producing insulin reactions, the sequelæ of which often incapacitated the patients for periods of from 24 to 48 hours. The shocks, unlike those following soluble insulin, were accompanied and followed by severe headache which was uninfluenced by the administration of carbohydrate, and which often lasted for several days. In 2 cases these shocks were accompanied by mental symptoms. All of these patients were on both protamine and soluble insulin, the total amounts varying from 55 to 140 units. The total amount of protamine insulin did not exceed 50 units in 4 of the cases, but in the 5th case 120 units were given. Of these 5 patients, 3 did fairly well for the first 6 months but the other 2 were never really adequately controlled.

In each of the 3 periods the total units of insulin required daily, the number of doses and the time over which the observations extended are recorded for each patient. Table 3 compares the status of the patient while on soluble insulin with his final status on protamine insulin and from this table one can readily see the patients in whom the diabetes was controlled. We have also noted in this table the tendency to shock, coma or infections during the period when the patient was on protamine insulin as compared to the period when he was on soluble insulin alone.

Of the 11 patients continued on protamine insulin, 8 (Cases 3, 4, 5, 7, 9, 10, 11, 14) still require additional soluble insulin varying from 10 to 60 units. In this group of patients, the number of injections of insulin required daily have decreased from 4 times on the soluble insulin to 1 or 2 on the combination, with the exception of 1 case who still requires 3 injections daily. Although this means that the patient needs to take insulin only twice during the day, the number of injections he has to make remains the same, as we have found it inadvisable to inject soluble insulin and protamine insulin at the same site. The total combined amounts of insulin in these cases were decreased in 5 of the patients. The decrease varied from 10 to 30 units daily. In 1 case there was no significant change in the total amount of insulin, and in 3 patients the combined amounts of soluble and protamine insulin were greater than the amount of soluble insulin required prior to protamine therapy. The increase was from 12 to 20 units daily. In 2 patients there was a gain of 10 and 20 pounds; in 2 patients there was a loss of 6 pounds; in the others, there was no change in weight. In 2 patients the tendency to insulin shock was diminished, and in 2 patients who had previously been admitted several times in diabetic ketosis there were no incidences of severe ketosis. The rest of the patients showed no significant change.

Of the entire group, only 3 patients have been adequately controlled finally on protamine alone (Cases 2, 12, 13). These 3

TABLE 3.—STATUS OF PATIENTS ON SOLUBLE AND ON PROTAMINE INSULIN.

Case No.	On Soluble Insulin.					On Protamine Insulin.				
	Diet in grams.			Weight changes.	Clinical condition of patient.	Diet in grams.			Weight changes.	Clinical condition of patient.
	Carb.	Prot.	Fat.			Carb.	Prot.	Fat.		
1	200	70	85	Constant	Admitted to hospital 7 times, either in coma or severe ketosis. Frequent insulin shocks. Very unstable.	250	70	85	Gain of 20 lbs. in 7 mos.	At start was fairly well controlled. After few mos. glycosuria became marked with occasional acetonuria, necessitating increase in insulin requirement. No admissions to hospital.
2	250	70	85	Constant	Four admissions to hospital for varying degrees of ketosis. Also having many insulin shocks. Chronic cholecystitis.	250	70	85	Gain of 17 lbs. in yr.	Occasional mild insulin shocks; mild consistent glycosuria. No further attacks of cholecystitis. Increase in protamine insulin needed.
3	250	75	85	Constant	Subject to insulin shocks with psychotic manifestations. Never in severe ketosis. No infections.	250	75	85	Constant	Occasional mild insulin shocks. Mild consistent glycosuria. Requirement for protamine decreased; soluble insulin increased.
4	200	75	85	Unable to gain	Subject to frequent insulin reactions and periods of marked glycosuria.	200	75	85	Gain of 10 lbs.	Fairly well controlled. No ketosis. Occasional mild glycosuria. No infection. Protamine insulin decreased, soluble insulin increased for control.
5	200	75	85	Unable to gain	Subject to frequent insulin shocks. Many upper respiratory infections. Never in severe ketosis.	200	75	85	Unable to gain	Occasional mild glycosuria. Frequent insulin shocks. Required increase in protamine insulin for control.
6	250	75	85	Slow gain	Frequently in shock or mild ketosis. Many upper respiratory infections.	250	75	85	Slight gain	Did well for first few mos., then had increasing glycosuria with acetonuria, alternating with severe shock. Protamine discontinued.
7	200	75	85	Gain of 30 lbs. in 4 yrs.	Occasional insulin shock or glycosuria. No infections.	200	75	85	Constant	Occasional mild insulin shock with occasional glycosuria. Status same as at outset.
8	200	65	85	Constant	Marked tendency to insulin shock. No infections.	200	65	85	Loss of 7 lbs. in past 6 mos.	Patient controlled at outset. Later had marked glycosuria and acetonuria and periods of severe insulin shock.
9	250	65	85	Constant	Stable. Occasional insulin shock and short periods of glycosuria.	250	65	85	Loss of 7 lbs. in 10 mos.	Controlled adequately. Slight decrease in protamine insulin.
10	300	75	85	Slow gain	Occasional insulin shocks.					

9	250	65	85	Constant	and short periods of glycosuria.					
10	300	75	85	Slow gain	Occasional insulin shocks. Well controlled.	300	80	85	Constant	Shows glycosuria. Protamine had to be discontinued and patient was returned to soluble insulin.
11	250	65	85	Constant	Pernicious anemia since 1932. Seven admissions to hospital for ketosis. Frequent glycosuria.	250	85	85	Loss of 6 lbs. in 4 mos.	Glycosuria present. No insulin shock. Soluble insulin had to be added for control.
12	350	75	85	No gain. Undernourished.	Six admissions to hospital in severe ketosis or coma. Easily thrown into shock by overactivity	350	75	85	Gain of 12 lbs. in yr.	Fairly well controlled. Moderate tendency to shock. Total units of protamine decreased. Does not require soluble insulin.
13	200	65	85	Constant	Well controlled.	200	65	85	Slow gain	Fairly well controlled. Only mild glycosuria or shock.
14	300	75	85	Unable to gain	Chronic sinusitis. Frequently in ketosis.	300	75	85	Slight gain	Chronic sinusitis unimproved. Protamine requirement increased. Moderate glycosuria.
15	200	65	85	Constant	Frequent insulin shocks. Subject to rectal abscesses recurring with ketosis.	200	65	85	Constant	Did well at onset. Diminution in shock after 9 to 10 mos. Had periods of marked glycosuria followed by prolonged insulin shocks which necessitated discontinuance of protamine insulin.
16	250	75	85	Slow gain	Numerous admissions to hospital for ketosis and infection.	250	75	85	Slow gain	Did fairly well at outset. Then had many head colds requiring increasing amounts of soluble insulin. Protamine discontinued.
17	250	75	85	Steady gain	Equal tendency to ketosis and shock. Numerous upper respiratory infections.	250	75	85	Constant	Patient observed in hospital for 2 mos. with frequent adjustments of protamine and soluble insulin unsuccessfully. Discontinued.
18	250	65	85	Slow gain. Undernourished	Two episodes of coma. Greatest tendency to insulin shock. No infection.	300	65	85	Early gain of 5 lbs.	Patient observed in hospital for over 2 mos. Unable to control successfully. Protamine discontinued.
19	295	115	150	Steady gain	Little difficulty in control.	300	80	85	Loss 10 lbs.	Observed in hospital for 1 mo. Unable to control successfully. Protamine discontinued.
20	350	80	120	Constant	Pulmonary tuberculosis with empyema. Fairly well controlled.	350	80	120	Constant	Observed in hospital for 1 mo. In spite of many adjustments unable to control successfully. Protamine discontinued.

patients have been apparently improved by the administration of protamine insulin. The improvement is evident in the following ways. The total number of doses required daily has been decreased from 4 to 2. Case 2, although still showing a mild glycosuria, has gained 17 pounds since the institution of protamine therapy. Case 12, previously subject to ketosis or shock, has had no admissions in shock, and although still showing a moderate glycosuria, feels very much improved. He has gained 12 pounds during the past year. Case 13 has gained a moderate amount of weight and has only a tendency to mild glycosuria or shock.

Discussion. There is no question in our minds that the 3 patients who are now controlled on protamine insulin alone have been definitely improved by this form of therapy. In addition, they have been spared the necessity of frequent insulin injections which is important to the patient. Of the remaining 17, we were unable successfully to transfer 4 patients from soluble to protamine insulin, and 5 were forced to discontinue protamine insulin after an adequate clinical trial of 8 months or more. Thus of the entire group, 9 patients, which is almost 50%, were unsuccessfully treated with protamine. In the remaining 8 patients it was necessary to use soluble as well as protamine insulin to control the diabetes. It seems to us that this is not a satisfactory procedure and that it is debatable whether or not these patients are any better off on this combination than they were on the soluble insulin alone.

When protamine insulin was first used in these patients there seemed to be some improvement and the number of doses of protamine insulin require daily was less than the number of doses of soluble insulin. The reason why this did not continue for more than about 6 months is problematical. One explanation that occurs to us is that repeated subcutaneous injections of protamine insulin may cause fibrosis of the underlying tissue and so interfere with uniform absorption of the protamine insulin. This is borne out by the fact that in many of the patients small nodules appear in the subcutaneous tissue after the prolonged use of protamine insulin. These are hard and firm and disappear slowly. Obviously, there must be an inconstant absorption of the protamine insulin to explain the alternating periods of glycosuria and shock which we observed in 5 of the patients. Perhaps the greatest disadvantage in the use of protamine insulin is the occurrence of insulin shock, of which the patient himself is unaware because of its insidious onset. One of the early manifestations of hypoglycemia induced by protamine insulin may be severe and intense headache which often persists for 48 hours. When protamine insulin is used, particular attention should be paid to the complaint of headache, bearing in mind that hypoglycemia may accompany it.

It is not our purpose in this report to detract from the value of an insulin preparation which can be absorbed slowly and therefore has a

definite theoretical advantage. We do feel, however, that a favorable response in the early period of protamine zinc insulin therapy does not necessarily mean that the patient will continue to be benefited. In evaluating the efficacy of protamine therapy it is necessary to observe the patients over prolonged periods and it seems to us that if improvement is not effected after a 6 months' trial, protamine insulin should be discontinued. Patients in whom protamine insulin is at first effective should be watched, after a few months, for evidences of irregular absorption and its ensuing alternating periods of severe glycosuria and hypoglycemia.

All the patients treated in this group were obviously severe diabetics, so that this was a searching test of protamine insulin. We have not attempted to substitute protamine for regular insulin when the patients required only 1 or 2 doses of insulin daily. It may be that patients requiring 2 doses daily could be reduced to 1 dose daily, in which case there would be an indication for substituting protamine for soluble insulin. Where the patient is controlled on one dose of soluble insulin daily we would doubt that there was any advantage in changing from the regular to the protamine insulin.

Summary. Twenty patients with diabetes mellitus, who had been observed for periods of 3 to 72 months on regular insulin in the diabetic clinics of this hospital, were transferred to protamine zinc insulin.

All of the patients treated were severe diabetics, 14 requiring 4 doses of soluble insulin daily and the rest 3 doses daily prior to the start of protamine zinc insulin.

It was impossible successfully to transfer 4 of the patients to protamine insulin and this form of therapy was discontinued at the end of 1 to 2 months. Of the remaining 16, after 8 months or more of protamine therapy, it was found necessary to return 5 of the patients to soluble insulin because of the occurrence of alternating periods of uncontrolled glycosuria and insulin shock. Of the remaining 11, 8 have required soluble insulin as well as protamine insulin in order to control the diabetes.

In 3 patients the diabetes was adequately controlled on protamine insulin alone. In only these 3 patients do we believe that beneficial effects followed the use of protamine insulin.

Since this paper was submitted for publication protamine insulin had to be discontinued in two more of the patients (Cases 10 and 14) because of increasing glycosuria. One additional case (No. 21) a 15-year-old girl, has been treated successfully with protamine alone for a period of 7 months making a total of 4 severe diabetics successfully treated with protamine alone. It may be of some significance that 3 of the successfully treated patients were found to have low basal metabolic rates of -15%, -20% and -22% (Cases 5, 12, and 21). It may be that lowered thyroid activity would tend

to render these patients more sensitive to the action of insulin. If this were the case, it would naturally follow that a more slowly absorbed insulin would be more effective and that less of it would be required to control the glycosuria. Possibly this may be one of the reasons for the successful response of some patients to protamine insulin.

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CHANGES IN THE GLUCOSE TOLERANCE TEST OCCURRING DURING AND AFTER INSULIN SHOCK THERAPY FOR SCHIZOPHRENIA.

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Many papers have appeared on the glucose tolerance test in the psychoses,[2,9,16,19–21,28] A survey of the literature has been summarized by McCowan and Quastel[21] in their statements: "On two points there is a general agreement: (1) The fasting blood sugar level of psychotic patients is generally within normal. (2) A disordered carbohydrate metabolism (*i. e.*, a lowered tolerance) is very frequently found in psychotic patients." In addition to the frequent disturbance in the tolerance to carbohydrates as reflected by the glucose tolerance curve, they found in their work some correlation between the mood of the patient and the blood sugar content in manic depressive patients but not in schizophrenics. More recent papers have reported no such correlation, and Gildea, Mailhouse and Morris[11] found an increase in blood sugar in normal persons under emotional strain but not during the emotional states of patients with mental diseases.

We are reporting the data from a study of the glucose tolerance curves of 22 schizophrenic patients ranging in age from 15 to 34 years, treated with insulin shock therapy and observed for varying periods up to 10 months after treatment. We feel that these changes are sufficiently marked to justify their presentation.

The technique followed for the insulin shock treatment is that outlined by Sakel.[23] Patients were usually given the treatment 6 days a week after reaching the coma dose, which ranged between 55 and 200 units.

Three-hour glucose tolerance tests were obtained before, during and after the course of treatment. After discharge from the hospital the patients reported at intervals for repetition of the glucose tolerance test.

Blood sugars were determined by a modification of the Folin-Wu method, after 1.5 gm. of glucose per kilo of body weight were ingested. In a few cases, glucose in amounts of 100 gm. was used when the weight of the patient could not be correctly determined. It is generally accepted that such variations in the amount of glucose ingested have no important effect on the curve obtained.

Table 1 presents observations on the 22 patients studied. As far as could be determined by careful physical and laboratory studies these patients showed no evidence of clear-cut disease other than schizophrenia. The following features seem significant to us: (*a*) The variation from the normal glucose tolerance in the pre-treatment glucose tolerance curves; (*b*) the hyperglycemic (diminished tolerance) type of curve that occasionally occurred during the course of shock therapy. (*c*) The hypoglycemic (increased tolerance) type of curve that occurred most frequently and more particularly at long intervals after treatment had been terminated.

Before treatment, 41% of our cases showed an abnormal curve. While there appears to be no obvious explanation, diet is one important factor which we feel should be stressed when dealing with psychotic patients and particularly those undergoing insulin shock therapy. A diminished dextrose tolerance subsequent to starvation has been observed in animals by du Vigneaud and Karr[10] and in humans by Himsworth[13] and others. The investigations of Sweeney[27] using different diets are particularly suggestive in this work. He showed that as a diet rich in fat decreased the tolerance, so did a diet rich in carbohydrate definitely increase it. The psychotic patient, whose delusions have altered his diet, is not uncommon. Further factors to be considered in explaining altered glucose tolerance are endocrine and toxic disturbances that may not fit any definite disease pattern.[7,8,14,24] To a lesser degree, exercise and muscular activity prior to the tolerance test affect the tolerance curves obtained.[26]

It will be seen from Table 1 and Fig. 1 that during treatment and as long as months after the last treatment the patient frequently

TABLE 1.—GLUCOSE TOLERANCE CURVES IN 22 SCHIZOPHRENIC PATIENTS BEFORE, DURING AND AFTER INSULIN SHOCK THERAPY IN RELATION TO TREATMENT DETAILS.

Case.	Date.	Blood sugar values in milligrams per 100 cc.					Relationship to treatment: days after last.	No. of treatments to date.	Coma dose.	Effect on schizophrenia.
		Fasting.	½ hr.	1 hr.	2 hrs.	3 hrs.				
	1937									
M. McD.	6-15	79	84	79	70	91	Before			
	7-1	87	112	116	59	61	Before			
	8-10	100	138	148	104	94	1	24	85 U	Fair
	9-18	100	123	116	79	89	2	43	110 U	
	11-18	59	100	96	82	72	62	43		
D. M.	7-21	109	118	161	100	96	Before	..	Up to	Good
	9-13	107	164	177	134	91	30	15	80 U	
A. C.	9-2	59	82	109	96	96	Before			
	10-13	82	82	68	61	54	23	6	Up to	Good
	10-29	70	100	91	70	54	39	6	75 U	
E. G.	7-23	112	177	150	153	150	Before			
	8-18	87	114	104	91	59	2	12	70 U	Good
	9-23	63	94	87	77	51	37	12		
	11-18	70	65	70	68	54	91	12		
L. A.	5-17	91	256	260	200	132	Before			
	7-20	87	240	248	121	82	1	40	70 U	Good
	8-11	77	161	100	77	49	8	30		
R. B.	1-7	75	79	127	118	75	Before	..	..	Good
	2-24	77	138	153	134	63	30	18	75 U	
	11-10	89	161	200	130	68	270	18		
	1936									
J. A.	12-30	84	180	143	84	49	Before			
	1937									
	2-5	84	112	138	87	63	15	27	85 U	Good
	7-27	77	132	71	77	32	222	27		
	9-10	79	107	82	68	63	263	27		
	11-11	75	109	98	70	72	294	27		
F. B.	1-5	75	158	177	138	104	Before	..	..	Good
	2-24	75	77	87	72	62	33	9	65 U	
	10-11	75	116	96	68	63	280	9		
R. L.	10-11	87	127	136	114	91	Before			
	10-25	72	109	125	98	59	Before			
	11-20	84	125	177	145	87	1	18	145 U	Good
	12-3	75	109	116	96	63	4	24		
	12-7	54	68	100	112	70	8	24		
M. P.	8-3	91	92	121	112	82	Before			
	10-22	77	94	150	116	104	14	50	60 U	Poor
	12-14	75	94	91	89	75	77	50		
A. K.	9-14	70	189	197	143	82	Before			
	11-2	68	145	132	96	87	1	22	110 U	Poor
	12-14	68	82	114	79	42	1	55	110 U	

Case	Date.	Blood sugar values in milligrams per 100 cc.					Relationship to treatment: days after last.	No. of treatments to date.	Coma dose.	Effect on schizophrenia.
		Fasting.	½ hr.	1 hr.	2 hrs.	3 hrs.				
N. B.	6-30	94	109	116	127	132	Before			
	7-6	132	145	200	230	177	Before			
	8-25	77	79	70	63	63	10	26	90 U	Good
	8-27	61	84	82	79	56	12	26		
	9-8	65	104	82	70	59	24	26		
	11-18	68	79	63	65	79	94	26		
J. W.	6-29	98	79	98	84	84	Before			
	7-6	82	109	107	89	70	Before			
	8-20	114	164	158	130	116	1	30	200 U	Fair
	8-30	92	116	138	89	63	3	34	200 U	
	9-7	79	109	91	77	54	4	35		
	10-7	82	132	109	68	84	34	35		
	11-10	79	136	100	87	107	67	35		
C. M.	6-28	77	123	112	102	123	Before	..	..	Good*
	7-6	79	132	153	118	100	1	5	130 U	
	7-20	91	123	114	98	75	3	12		
	9-11	89	96	77	59	70	43	18		
M. N.	7-16	65	82	118	193	177	Before			
	9-21	77	116	94	63	68	2	26	60 U	Good
	10-22	65	123	82	79	72	1	51	65 U	
	12-7	63	87	84	72	72	40	51		
J. L.	8-10	65	132	134	100	82	Before			
	9-16	68	125	96	72	51	1	23	105 U	Fair
	9-22	94	130	148	94	56	1	27	105 U	
	12-4	72	84	111	102	68	43	40		
D. T.	8-25	91	138	118	87	84	Before			
	9-16	68	114	132	100	91	1	3	75 U	Poor
	11-23	76	96	125	72	68	39	16		
	10-14	70	94	109	77	87	3	16		
A. Z.	5-24	109	123	91	89	84	Before			
	8-14	91	184	134	121	114	1	47	75 U	Good*
	9-20	75	82	96	72	89	6	69	90 U	
	11-24	75	127	82	72	40	71	69		
L. P.	9-2	68	82	77	77	77	Before			
	9-7	68	70	77	65	69	Before	..	..	Fair
	10-22	59	72	75	100	72	1	28	175 U	
	12-8	54	77	65	65	59	19	49		
M. K.	9-22	77	116	134	138	100	Before	..	..	Poor
	11-24	68	118	100	97	89	1	44	115 U	
	12-10	63	87	94	116	96	1	54	120 U	
D. S.	10-21	123	136	138	114	100	Before			
	12-13	54	72	91	94	82	1	20	160 U	Good
M. S.	8-5	112	145	100	96	82	Before			
	8-26	75	100	150	84	98	1	15	55 U	
	9-10	75	112	82	77	69	12	16	55 U	Good*
	10-2	75	116	116	96	89	3	28	55 U	
	10-18	70	82	104	82	63	2	37	70 U	
	11-24	82	98	91	87	75	1	59	95 U	
	12-13	59	89	77	75	77	1	70	110 U	

* Relapse after discharge.

showed a hypoglycemic type of curve. This occurred in 73% of the cases. Three of 4 patients followed for 10 months after the termination of treatment showed this type of response to repeated tests, while 7 of 8 patients followed for 2 to 4 months still showed an increased tolerance with the curve hypoglycemic in type. It was the most consistent finding in our data. The patient, at this time, was often out of the hospital, adjusted to a different environment, not infrequently working and partaking of no special diet. The reference to diet is emphasized again because the patients during the course of therapy were given high carbohydrate diets to counteract any possibility of "after shock." This, as mentioned before,

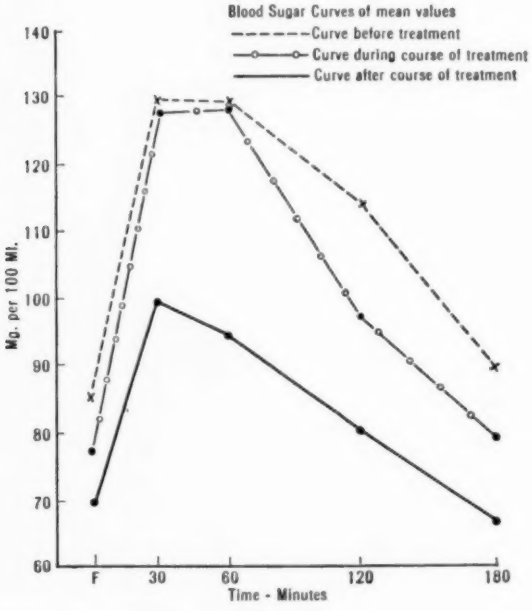

FIG. 1

might lead to the increased tolerance type of curve. We could discover but one reference to a similar finding in the literature. Müller[22] in a thorough review of insulin and metrazol treatment states that he has found spontaneous hypoglycemia occurring after treatment is terminated, and gives it as one of the bits of evidence for humoral changes occurring after insulin treatment.

During the course of therapy in 4 patients, a markedly hyperglycemic type of curve was obtained. In 3 patients these curves were obtained during the day immediately following a treatment day; in 1, 30 days after the last treatment. This patient did not return for subsequent check-up. This is the type of curve that has

recently been reported by Looney and Cameron[18]. In 7 of the 9 cases studied by them the tolerance was measured the day after the last treatment. They suggest that the change may be due to the stimulation and sensitization of the adrenal mechanism, since it has been shown by Cannon, McIver and Bliss[5] and Britton, Geiling and

TABLE 2.—BLOOD SUGAR RESPONSES TO 1 CC. OF ADRENALIN (1:1000) INTRAMUSCULARLY IN 16 SCHIZOPHRENIC PATIENTS.

Case.	Blood sugar values, milligrams per 100 cc. Fasting.	10 min.	30 min.	60 min.	Date, 1937.	Comparative trend of post-treatment curve.
A. K.	63	79	94	104	9-30	
	77	82	87	116	12-24	Increase
M. C.	68	79	100	100	8-21	
	54	70	82	104	12-22	Increase
C. S.	61	77	150	145	9-16	
	75	109	116	114	12-27	Decrease
N. B.	100	104	132	200	7-7	
	79	134	123	77	8-26	Decrease
P. G.	84	82	89	112	8-2	
	75	87	96	100	8-20	Decrease
M. H.	77	77	132	121	10-8	
	72	75	141	132	11-20	Increase
R. L.	65	84	100	125	9-25	
	70	87	123	143	11-30	Increase
C. M.	84	87	134	180	6-28	
	89	107	145	109	7-21	Decrease
D. M.	84	89	112	132	7-23	
	65	75	89	98	9-18	Decrease
M. McD.	87	82	82	107	6-28	
	91	96	87	91	8-18	
	68	72	123	116	9-27	Decrease
S. P.	70	89	96	164	4-15	
	77	100	102	125	5-26	
	84	94	114	118	7-23	Decrease
C. R.	75	94	134	177	7-28	
	75	109	107	141	8-25	Increase
J. W.	65	82	89	82	7-10	
	79	79	82	87	9-15	
	63	77	116	130	9-18	Increase
L. A.	91	109	150	161	5-22	
	77	91	124	77	8-10	Decrease
D. T.	72	84	87	96	8-27	
	54	87	91	114	12-21	Increase
J. L.	72	79	96	145	8-7	
	70	116	134	200	12-18	Increase

Calvery[4] that hyperadrenalinemia occurs after insulin shock. The duration of this state, however, after the insulin shock has been remedied does not seem to have been determined. It is possible that hyperadrenalinemia may persist for days and thus explain these findings. It must be recalled that previous insulin administration has been shown to cause a temporary loss of tolerance for carbohydrates in normal individuals. The duration of this effect is said to be 2 to 3 days.[1,6,29] However, the glucose tolerance curves obtained long after treatment had been terminated are of a different type and are not satisfactorily explained by this hypothesis.

Soskin, Allweiss and Cohn[25] maintain that it is the liver and not the pancreas which is the most potent factor in determining the nature of the dextrose tolerance curve. They state, "Results show that there is no appreciable store of insulin in the tissues by which the dextrose may be affected once the pancreas is removed. . . . It is obvious that although the liver is a major factor in determining the dextrose tolerance curve, it can respond normally to sugar administration only when under the influence of a suitable endocrine balance."

That liver insufficiency, if present, is not pronounced, is suggested by normal results of bromsulphalein tests, by absence of a significant change in serum albumin or globulin and by normal cholesterol—cholesterol ester ratios.

Following a course of therapy we have found a definite tendency toward lower basal metabolic rate (calculated from oxygen consumption) in the majority of our patients. Again, diet may be a factor in explaining this change, since diets given during the course of treatment were far richer in carbohydrates than those before treatment. This change in diet may alter the respiratory quotient sufficiently to influence basal metabolic rate calculations. Although increased glucose tolerance is the usual finding in hypothyroidism and hypopituitarism, these patients did not show any of the obvious signs of the hypo-function of these glands. However, the possibility that depression of pituitary function may occur is one that we are pursuing with further studies. In this connection, the recent work of Long,[17] on the control of adrenals through the pituitary, is significant. Increased pancreatic activity with hypersecretion of insulin is not a plausible explanation since it is accepted that administration of a hormone leads to diminished endogenous secretion of that hormone and not to increased hormonal production.

That hypoglycemic sugar tolerance curves in response to insulin shock therapy are not peculiar to schizophrenia is suggested by the studies on a small group of patients with manic depressive (depressed) psychoses and a case of dementia paralytica. In all of these cases a hypoglycemic type of response was obtained after treatment.

Finally, the glycemic response to adrenalin was determined before

and after a course of therapy on a series of patients. One cubic centimeter of 1:1000 adrenalin was given intramuscularly to the fasting patients. Blood sugar determinations were made before injections and 10 minutes, 30 minutes and 1 hour after injection. (Blood pressure and pulse reading were obtained at 5-minute intervals.) This test was formulated in an attempt to determine possible diagnostic changes in the response of the adrenal-sympathetic system as a result of prolonged administration of insulin[12,15] and also as a possible indicator of liver function.[3] While the majority of curves "after-treatment" show a continuous rise of blood sugars which may be higher than those in the "pre-treatment" curves (Table 2), the findings on the whole do not offer convincing evidence for a sensitization of the adrenal-sympathetic mechanism.

We believe that the tendency toward spontaneous hypoglycemia is probably reflected in the increased appetite, resulting in marked progressive weight gain seen in these patients months after the treatment has been terminated. It may also explain the atypical hypomanic reactions that occur infrequently after treatment in some of these patients. However, it does not seem to be related to the possible therapeutic outcome of the disease. The similar type of response shown by the other forms of mental disease suggests that this form of therapy does not owe its effect to an influence upon a fundamental endocrine disturbance peculiar to schizophrenia.

Summary and Conclusions. 1. The glucose tolerance curve is abnormal in a relatively high percentage of our cases of schizophrenia. This is in agreement with the findings of most of the workers in the field.

2. During and following the course of insulin shock therapy we have noted definite changes in the character of the glucose tolerance curve. A biphasic variation in the type of curve is suggested. During a course of treatment, particularly immediately after a course of treatment has been terminated, a hyperglycemic (diminished tolerance) type of curve is at times obtained. However, in many patients immediately, and in most, many days and months after the treatment has been terminated, a hypoglycemic (increased tolerance) curve prevails. Ten of 12 patients followed from 2 to 10 months after their last treatment showed this type of response.

3. These findings are probably not peculiar to schizophrenia in its therapeutic response to insulin therapy, nor are they of prognostic value.

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THE EFFECT OF BENZEDRINE ON CILIARY MOVEMENT.

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In a previous communication,[2] benzedrine (benzyl-methyl-carbinamine) was administered as an inhalant and was found to relieve nasal congestion in patients afflicted with coryza but not to affect the duration of the cold. At the same time, a 0.1% aqueous solution of the sulphate of benzedrine was found to decrease the movements of cilia in the mucosa lining the pharynx and esophagus of frogs. The object of the present further investigation was to ascertain if the free base of benzedrine, which was that form used by inhalation in the former work,[2] had an effect on cilia similar to that of the sulphate of benzedrine which was the substance whose effect on cilia was studied and reported at that time.

Some otolaryngologists are—and some are not—concerned about the possible harmful effects to the mucous membrane of the nose and throat of repeated use of recently proposed preparations containing vasoconstrictor drugs such as epinephrine, ephedrine, benzedrine or meta-synephrine in the local treatment of coryza. By local vasoconstriction, these preparations give to the patient an immediate pleasing relief from "stuffiness of the head." The effect wears off after some minutes or at most in an hour or two and the patient again applies the remedy. The cold runs its usual course but the patient is free of the distressing and exasperating symptoms of nasal turgescence. It is reasonable to ask, therefore, whether the harmful effects of these substances on mucous surfaces, which are probably slight from *single* applications, should be neglected in view

of the immense relief experienced by the patient. Apropos of this question, it may be recalled that the recognized treatment of many surface lesions involves application of substances which are known to destroy or harm tissue.

There is a further possible factor to be considered. Some believe that the congestion of the nasal mucosa is Nature's method of combating colds by asphyxiating the virus of coryza through inhibiting or preventing the passage of air through the nasal cavity.[3] Should this theory be true, then the nasal passage presumably should not be opened by vasoconstrictors. The situation may prove to be analogous to the relation between antipyretics and fever, antipyretic drugs having considerably less use now than formerly.

TABLE 1.—THE EFFECT OF TOPICAL APPLICATION OF SEVERAL SYMPATHOMIMETIC SUBSTANCES UPON CILIARY MOTION OF THE ESOPHAGEAL MUCOSA OF FROGS.

Substance.	Concentration, %.	Average percentage depression of ciliary motion after:			Percentage of experiments showing depression.
		1 min.	2 mins.	3 mins.	
Benzedrine	0.05	38	44	44	92
Benzedrine sulphate	0.05	32	36	36	83
Benzedrine	0.1	46	48	52	92
Benzedrine sulphate	0.1	38	42	47	92
Meta-synephrine hydrochloride	0.1	17	23	25	75
Ephedrine hydrochloride	0.1	25	25	32	88

Method. The procedure used in this further experimental study of benzedrine was identical to that previously reported.[2] The effect of a number of related drugs on ciliary motion was evaluated by comparing the rate at which cilia lining the esophagus of the frog carried a light object a given distance before and after application of a solution of the drug. To facilitate interpretation of results, a slightly different method has been used to summarize them. The average passage time of not less than 24 and not more than 32 experiments was calculated before applying a solution to be tested and after the end of 1, 2 and 3 minutes after applying the solution. The initial average was then subtracted from the average at the end of 1 minute, this difference was divided by the average at the end of 1 minute and multiplied by 100 to give the percentage change in the rate of ciliary motion. Corresponding percentage changes were calculated at the end of 2 and of 3 minutes. These mean percentage changes have been assembled in Table 1. To show the regularity with which ciliary motion was depressed by all of the solutions studied, the number of experiments in which depression was obtained was calculated as a percentage of the total number of experiments and these latter figures are listed in the last column of Table 1.

After the third reading had been obtained, the mucosa was washed with saline and further passage times recorded. In the majority of instances, the cilia recovered from the depressant effects of the solutions applied, though recovery was seldom complete. This observation, however, formed the basis of the previously made statement that a *single* application of these sympathomimetic compounds probably has little permanent effect upon ciliary movement.

Results. Six solutions were tested and in the concentrations noted in Table 1. In comparable concentration, meta-synephrine

or neo-synephrin was found to have the least depressant effect, confirming an earlier report.[1] Ephedrine hydrochloride averaged 25 to 50% more toxic in this respect than meta-synephrine. Benzedrine sulphate was correspondingly 80 to 120% more toxic and the free base of benzedrine, which was that form used as an inhalant in our previous work,[2] was 100 to 170% more toxic on the average. Both in a concentration of 0.05 and 0.1%, benzedrine was found more toxic than benzedrine sulphate. A part and possibly a large part of this increased toxicity of the free base of benzedrine may undoubtedly have been due to the fact that a given percentage solution of the free base contains more benzedrine than the same concentration of benzedrine sulphate, the molecular weight of the latter substance being greater than that of the former.

Conclusion. In concentration of 0.05 and 0.1% in distilled water, the following sympathomimetic compounds were found depressant towards ciliary movements of the esophageal mucosa of frogs and in the following order of decreasing toxicity: benzedrine, benzedrine sulphate, ephedrine hydrochloride and meta-synephrine or neo-synephrin hydrochloride.

Substances used in this work were generously provided as follows: benzedrine and benzedrine sulphate by the Smith, Kline and French Laboratories; ephedrine hydrochloride by the Abbott Laboratories; neo-synephrin hydrochloride by Frederick Stearns & Co.

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THE ANTIDOTAL ACTION OF PICROTOXIN IN ACUTE INTOXICATION BY THE BARBITURATES.

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There are accumulated sufficient experimental data to establish picrotoxin as an active antidote for acute poisoning from derivatives of barbituric acid. In sublethal doses of these compounds, picrotoxin shortens the recovery time; in lethal doses, within certain limits, it prevents death; and, when hopelessly large doses have been given, it prolongs the life of laboratory animals.[1, 6b, 7, 8]

Recent controlled clinical studies[2] and case reports[3–6, 9] have established picrotoxin as an effective physiologic antidote for barbituric acid intoxication in humans.

Four case reports are herein presented as examples of the clinical effectiveness of picrotoxin,* and to outline briefly the therapeutic procedures found most efficacious.

* The picrotoxin used in these studies was supplied through the courtesy of the Abbott Laboratories, Inc.

Cases reported are those in which the drug and amount taken could be established with reasonable accuracy.

Case Reports. Case 1.—A white female, aged 24, swallowed 114 gr. of sodium amytal. Twelve hours later a hotel physician treated the patient. A gastric lavage was done, strychnine gr. 1/40 and coramine 3 (2 cc.) ampules were given intramuscularly. The patient was brought to the hospital soon thereafter since the physician believed pulmonary edema was developing.

Examination on Admission. The patient was in coma with completely relaxed, flaccid musculature. There was no reaction to painful stimuli. Superficial and deep reflexes were absent. The pupils were 3 mm. in diameter and did not react to light. The skin was cyanotic, hot and dry. Rectal temperature was 102° F. The airway was obstructed, mucus was profuse in the pharynx and signs of pulmonary edema were present. Respirations were shallow, the rate 36 to 40 per minute. Pulse rate, 120; blood pressure, 110/60.

Treatment and Course. A tube was introduced into the stomach and a thorough lavage with a solution of sodium bicarbonate was done. A spinal puncture was done and the patient was catheterized. A soft rubber endotracheal airway was placed translaryngeally and the lower respiratory tract cleared of mucus by suction. An intravenous infusion of 5% glucose in normal saline was instituted. Picrotoxin was given in 3 mg. doses by way of the infusion tube at irregular intervals. From 10 A.M. to 7 P.M. 129 mg. were administered. The early doses resulted in deeper respirations only. The later doses were followed by twitching of the facial muscles. Shortly after 7 P.M., the patient moved her head and legs. She slept throughout the night but could be stimulated to open the eyes and move the head or extremities. At 7 P.M., the patient was reacting on the endotracheal airway. It was removed and the patient moved her body. At 1 P.M. there was verbal response to questions and the patient complained of a sore throat and numbness in both hands. Convalescence was uneventful thereafter. The patient was discharged on the fourth hospital day. At discharge, there was a bilateral ulnar palsy.

Case 2.—A white female, aged 28, 8 hours prior to admission had taken 90 gr. of sodium pentobarbital together with some lemon extract and gin.

Examination on Admission. Patient was in coma and did not react to painful stimuli. The superficial reflexes were absent, the deep reflexes sluggish. Eyeballs were fixed centrally, pupils 2 mm. in diameter did not react to light. The respirations were shallow at a rate of 30 per minute. The airway was obstructed with mucus and from edema of the vocal cords. There were moist râles throughout the chest. Rectal temperature, 99° F.; pulse rate, 140; blood pressure, 110/80.

Treatment. Catheterized, gastric lavage, and intravenous infusion with 5% glucose in normal saline started. A soft rubber endotracheal airway was put in place and the respiratory tract cleared by suction. Forty-eight mg. of picrotoxin were given intravenously during the next hour. Respirations were stimulated, there were twitchings about the mouth followed by retching and vomiting. Patient slept throughout the day and night. The following morning was aroused and found to be rational. Recovery was complete on the third day when she was discharged.

Case 3. White female, aged 45. Two years previous to present hospital admission had thyroidectomy for advanced Graves' disease. For past 4 months had acted strangely, drinking large amounts of alcohol and taking luminal. On the day of admission fell on the street unconscious and was taken home. At midnight was brought to the hospital. She had received 15 gr. of caffein sodium benzoate and on admission was given 1.5 cc.

coramine intravenously. She had taken at one time (noon) 75 gr. of sodium luminal.

Examination on Admission, 1.30 A.M. Patient in coma with no response to painful stimuli. There was a thick, mucoid froth in mouth and coarse râles throughout the chest. The skin was warm, cyanotic and perspiring, the pupils were equal, regular and reacted to light and accommodation. Respirations were rapid and stertorous. Deep reflexes were absent. Pulse rate was 140, the rectal temperature 100° F.

Treatment. Patient was catheterized and the stomach lavaged. An intravenous infusion of 5% glucose in normal saline was started. Oxygen therapy by oropharyngeal insufflation, 6 liters per minute, was instituted. An active laryngeal reflex hindered using an endotracheal catheter. Picrotoxin, 1 mg. per minute, was given by way of the infusion tube, beginning at 2.30 P.M., until 15 mg. were given. This amount caused the eyeballs to oscillate, the patient to react to painful stimuli and within 5 minutes to talk incoherently. Infusion was discontinued. At 7 A.M. the patient was again in deep coma. Infusion was started and 30 mg. of picrotoxin were given intravenously during the next 30 minutes. The patient reacted to pain and began moaning. Gastric lavage was done and calomel, 1 gr. in 10 cc. water, was left in stomach. Mercupurin (1 cc.) was given intramuscularly. At 10.15 A.M. patient was in deep sleep. Eight mg. picrotoxin given intravenously caused muscle twitchings. Then 3 mg. doses of picrotoxin were given intramuscularly every 10 to 30 minutes. At 7 P.M. patient could be aroused easily and responded to spoken questions. No treatment was attempted during the night. The following morning the patient was stuporous but moved the arms and legs. An additional 3 mg. of picrotoxin were given intramuscularly. This completed a total of 122 mg. given during treatment. At 11 A.M. the patient was alert. The following day (4th) she was transferred to the Psychopathic Service where a diagnosis of involutional melancholia with suicidal tendencies was made.

CASE 4.—A white male, aged 57, attempted suicide by taking 500 gr. of sodium barbital (veronal) by mouth during the late afternoon. He was admitted to the hospital at 1.00 A.M., having received no treatment except $\frac{1}{12}$ gr. of strychnine.

Examination on Admission. An obese male in coma with flaccid, relaxed muscles did not react to painful stimuli. Reflexes were absent. The pupils dilated, centrally fixed and non-reactive to light. Respirations were 16 per minute. There were no chest râles and little mucus. The pulse rate was 100; blood pressure, 100/60; temperature, 98° F. (rectal).

Treatment. Gastric lavage and lumbar puncture done. The spinal fluid was clear and without increased pressure. An indwelling urethral catheter was inserted. A soft rubber endotracheal airway was put in place. An intravenous infusion of 5% glucose in normal saline was started. Picrotoxin, 23 mg., was given by the infusion tube at the rate of 1 mg. per minute. There was an increase in respiration and slight twitching about the eyes and mouth. The patient soon returned to the previous state, and an additional 24 mg. of picrotoxin were given at the same rate. At 8 A.M. deep coma was again evident and 21 mg. of picrotoxin were given. At 10 A.M. 39 mg., given 1 mg. per minute were required to elicit twitching about the mouth. At noon 12 additional mg. of picrotoxin produced slight tremors. By 8 P.M., the patient was again in deep coma. Picrotoxin was given at intervals throughout the night and next day. A very slow infusion was continued, gastric lavage was done at frequent intervals and sodium bicarbonate solution left in the stomach each time. On the third day, 9 to 9.30 A.M., 24 mg. of picrotoxin were given. The patient then responded to painful stimuli, opened his eyes and reacted on the endotracheal tube. Following this it was possible to arouse the patient with intravenous picrotoxin but

after an hour or more he would return to the comatose state. Then intramuscular injections of picrotoxin were given in an attempt to maintain the patient so that he would react to painful stimuli. This required about 20 mg. per hour. This schedule was continued for 20 hours and the patient was definitely more active. The endotracheal airway was removed and replaced often during the 4th and 5th days. During the next day the airway was not used, some fluids were given by mouth and the infusion was discontinued. Intramuscular picrotoxin was decreased to 10 mg. per hour. Late that day (6th) the patient responded to spoken questions but was very stuporous. During the late evening, it was again impossible to arouse the patient. He was given 42 mg. of picrotoxin intravenously within 2 hours and then became more alert than at any previous time. He answered questions readily. Intramuscular picrotoxin was resumed at 12 mg. per hour. The following morning (7th day) the patient talked clearly, took fluids by mouth and moved his arms and legs at will. Mercupurin was given to increase urinary output. Picrotoxin was discontinued. By noon he was again in a somnolent state, difficult to arouse. Intramuscular picrotoxin (20 mg. per hour) did not produce the effect it had previously. Late in the day it was necessary to give intravenously 30 mg. of picrotoxin to arouse the patient. He then talked easily, and took nourishment. He was engaged in conversation for nearly an hour and told of his schooling, war experiences and troubles. He received no picrotoxin during the night. At 7 A.M., it was impossible to arouse him. He was given 30 mg. of picrotoxin intravenously in 30 minutes' time; this produced a generalized convulsion lasting several minutes. The convulsion was finally controlled by giving 7 gr. of sodium amytal intravenously. Soon thereafter, 27 mg. of picrotoxin were given by vein and the patient responded sluggishly. He appeared very weak, although he could be aroused. Thereafter, he gradually became weaker, circulatory depression was evident, respirations slowed and became shallow. He expired on the 8th hospital day. A total of 2134 mg. of picrotoxin was given. There was 10.2 mg. of barbiturate in 20 cc. of urine collected shortly before death.

Autopsy, which unfortunately did not include the brain, revealed acute hepatitis and hypostatic pneumonia. The liver (500 gm.) contained 27.8 mg. of barbiturate and traces of picrotoxin.

Discussion and Summary.—The physical signs and symptoms in each case reported indicated severe poisoning from barbiturates. The amount of drug taken was in each case well within the range considered fatal. The patient who did not recover had received an amount that is usually regarded as hopelessly fatal. The experience with these patients suggest that in human beings, results with picrotoxin in barbiturate poisoning may be anticipated which are identical with those found by Tatum[8] and his co-workers in laboratory animals.

In the management of patients with severe barbiturate intoxication, too much emphasis cannot be given to the therapeutic procedures in addition to picrotoxin therapy. Active, close supervision is essential. Frequent changes in position; maintenance of body temperature; support of circulation and nutrition with intravenous fluids; frequent gastric lavage and feeding; frequent catheterization; diuretics; blood transfusion; oxygen therapy and the use of an endotracheal airway; frequent cleaning of trachea by suction through the airway are indicated and their importance is not surpassed by the use of picrotoxin.

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PROTHROMBIN DEFICIENCY AND THE BLEEDING TENDENCY IN OBSTRUCTIVE JAUNDICE AND IN BILIARY FISTULA.

EFFECT OF FEEDING BILE AND ALFALFA (VITAMIN K).*

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IT is well known that a bleeding tendency often develops in patients suffering from chronic biliary obstruction. Epistaxis and bleeding from gums and other mucous surfaces are of common occurrence. The surgeon frequently encounters persistent bleeding at the operating table, or from the wound afterwards. Such hemorrhage often is difficult to control, even with repeated transfusions. As a rule, the coagulation time is found to be but little in excess of normal. The bleeding time is often moderately prolonged, especially if determined by the method of Ivy.[7] Many views have been held regarding the nature of the disturbance. Almost every clotting factor has been said by one writer or another to deviate from normal. Antithrombin has been thought by some to be excessive. One of the more popular views has been that a disturbance in calcium metabolism is responsible for the bleeding; however, calcium therapy has not been found to be particularly effective. Quick, Stanley-Brown, and Bancroft[10] found that tissue juice accelerates the clotting of normal plasma more than in the case of jaundiced plasma, and they suggested that the jaundiced plasma is deficient in prothrombin.

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Their proof is incomplete, however. A recent review by Ravdin and Johnston[11] leaves the cause of bleeding in these cases an open question. Very recently considerable speculation concerning the possible rôle of vitamin K has been stimulated by the work on "hemorrhagic chick disease."

Much of the present confusion regarding the bleeding tendency in obstructive jaundice is due to lack of quantitative analysis. We have given particular attention to the development of technique for the titration of prothrombin. We have finally succeeded in developing a method[12,13] which is independent of variables inherent in other methods. With the aid of this technique we have studied the plasma prothrombin in a number of cases of biliary tract disease, some of which had a definite tendency to bleed. We have also been able to follow the prothrombin levels during recovery and to study the effect on the prothrombin level of feeding bile, and alfalfa extract rich in vitamin K.

Methods. The prothrombin method used has been previously described.[13,12]

The alfalfa extract used to supplement bile feeding was prepared from dry alfalfa meal (sun-cured). The solvent used in making the extract was a special lead-free, low-boiling petroleum ether known commercially as "Skellysolve A." The dry alfalfa meal was placed in flasks and extracted in series, after which the solution was filtered and concentrated by distillation. Prior to use, this concentrate was evaporated to dryness (a thick greenish greasy residue), and emulsified in human bile or in 2% bile salt (sodium taurocholate). This preparation was given by mouth in the early evening hours in doses corresponding to 200 to 400 gm. of the alfalfa meal per day. Samples of the extract were tested for their curative effect in "hemorrhagic chick disease" and found to be highly potent.

Plasma Prothrombin Level and Bleeding Tendency in Obstructive Jaundice. Table 1 shows the plasma prothrombin levels in 27 cases of obstructuve jaundice. In most cases, the level was definitely below normal. However, the amount of lowering is not clearly dependent upon the intensity or duration of the jaundice.

In this series, 6 showed a definite bleeding tendency. This tendency in every instance was associated with a marked decrease in the prothrombin level, usually to less than 35% of normal. Later determinations in the cases which recovered showed that cessation of bleeding was associated with an increase in the prothrombin values.

A few cases develop very low prothrombin values and yet escape actual bleeding. In Patient 26, for example, no hemorrhage occurred, although the prothrombin fell to 37% of normal. Also, in Patient 25 there was no bleeding even though the prothrombin level fell to 20% 11 days after operation. Such cases are, however, definitely in the danger zone and serious bleeding is to be feared, especially if any operative procedure is anticipated. In several of the cases in which extensive bleeding occurred, the bleeding

tendency did not become manifest until the time of operation or shortly thereafter.

TABLE 1.—PROTHROMBIN LEVEL IN OBSTRUCTIVE JAUNDICE.

Case.	Cause of obstruction.	Serum bilirubin, mg. %.	Duration of jaundice.	Prothrombin, %.	Bleeding tendency.
1	Carcinoma of pancreas	23	4 mos.	37	Excessive bleeding, paracentesis wound
2	Common duct stone†	5	1 mo.	60	None
3	Cholangiitis; abscess, head of pancreas*	4.6	?	23	Epistaxis; profuse bleeding at operation
4	Cholelithiasis*	9.8	4 mos.	69	None
5	Common duct stone†	12	?	71	None
6	Carcinoma, head of pancreas	31	3 wks.	49	None
7	Chronic cholangiitis(?)*	24	7 wks.	62	None
8	Carcinoma of pancreas; common duct stone*	18	1 mo.	84	None
9	Common duct stones†	14	1 wk.	57	None
10	Common duct stone*	6	2 mos.	80	None
11	Common duct stone*	8.4	6 mos.	79	None
12	Common duct stone*	3.2	5 days	91	None
13	Common duct stone(?)	5	2 wks.	77	None
14	Cholelithiasis*	‡	?	89	None
15	Common duct stone(?)†	8.4	5 wks.	64	None
16	Cholelithiasis*	21	4 wks.	84	None
17	Common duct stones†	18	?	70	None
18	Common duct stone(?)*	6.8	5 mos.	52	None
19	Carcinoma, ampulla of Vater*	29	4 wks.	66	None
20	Carcinoma of pancreas	10	3 wks.	60	None
21	Cholangiitis(?)*	21	2 mos.	34	Bruised easily; bled from gums
22	Carcinoma of pancreas†	34	4 wks.	17	Bled excessively from operative wound
23	Common duct stones*	..	6 wks.	16	Bled markedly from operative wound
24	Carcinoma of biliary tract*	23	8 wks.	10	Bled markedly from operative wound
25	Common duct stone*	11	1 wk.	51	None
26	Common duct stone(?)	29	4 wks.	37	None
27	Common duct stone*	17	6 wks.	50	None

* Denotes operative diagnosis. † Denotes autopsy diagnosis. ‡ Icterus index, 43.

Biliary Fistula: Prothrombin Level and Bile Feeding. Patients having chronic biliary fistulæ, even though there is no jaundice, at times develop a tendency to bleed similar to that seen in cases of obstructive jaundice. We have recently had the opportunity of following the prothrombin level in such a case and of studying the effect of bile feeding on the plasma prothrombin.

Case Abstract. A white woman, aged 66, had a biliary fistula of 4 months' duration. The fistula had developed following the removal of an acutely inflamed gall bladder. During this entire period the stools were acholic. On admission to this hospital there was slight jaundice. For 3 weeks pre-operatively about one-half of the bile which drained from the

fistula was given back by mouth. During this time the prothrombin varied between 58 and 45%. At operation, February 12, 1937, reconstruction of the stenosed common duct was found to be impossible and the fistula was enlarged for better drainage. Following this operation there was a further decrease in prothrombin to 27% and there was bleeding from the wound on the 4th and 5th postoperative days. This was controlled by a transfusion. Starting on the 12th postoperative day and continuing for 6 weeks, about 400 cc. bile per day were given by mouth. This represented two-thirds of the bile which drained from the fistula. The patient steadily improved and was discharged at the end of 7 weeks.

The plasma prothrombin response to bile feeding is shown in Chart 1. The prothrombin gradually rose to a nearly normal level over a period of 6 weeks.

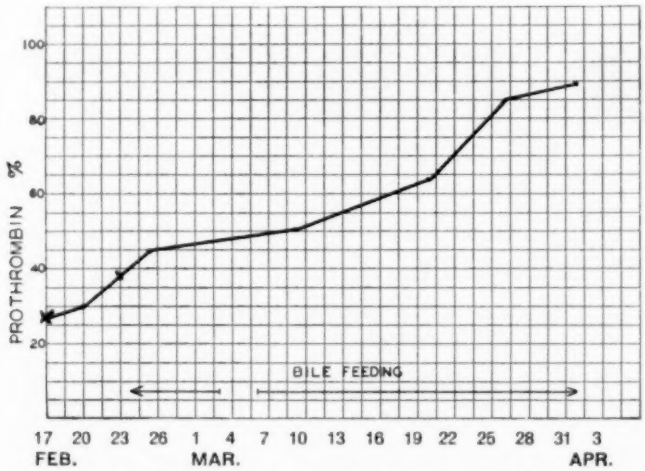

CHART 1.—Biliary fistula. Prothrombin response to bile feeding.

Effect of Bile and Alfalfa Extract Feeding on the Prothrombin Level in Obstructive Jaundice. We have studied the effect of feeding bile or bile salts supplemented with a fat soluble extract of alfalfa on the prothrombin level in a number of cases of obstructive jaundice with hypoprothrombinemia. Four of these cases are shown in Chart 2.

Case Abstracts. CASE 21.—A white woman, aged 48, had painless jaundice with acholic stools for 2 months. During the week before admission here, she bruised easily and bled from the gums at times. The day after admission, March 21, 1937, the van den Bergh test showed 22 mg. bilirubin and Duke's bleeding time was 14 minutes. On March 25 and March 31, blood transfusions of 500 cc. were given and from March 29 to March 31, 200 to 300 cc. bile were fed daily. The bleeding tendency persisted, however. During this time the plasma prothrombin was at a low level. It rapidly increased to a nearly normal level with addition of alfalfa extract (equivalent 400 gm. alfalfa meal emulsified in 100 cc. human bile daily), as shown in Chart 2. No further bleeding occurred. At operation, April 7, the obstruction, apparently high in the liver hilus, could not be relieved, and the jaundice was still present at the time of discharge, April 23.

Case 25.—An obese white woman, aged 52, had had attacks of right upper abdominal pain with radiation to the back for the past 10 years. The attacks increased in severity and frequency during the past 3 months, and she was intolerant of fatty foods. On April 1, 1937, jaundice and acholic stools were first noted. On April 6, van den Bergh test showed 11 mg. serum bilirubin. Because of a subnormal plasma prothrombin level, she was given alfalfa extract for a 5-day period (400 gm. equivalent daily, emulsified in 100 cc. human bile for first 3 days, in 30 cc. 2% sodium taurocholate for last 2 days). The plasma prothrombin rapidly increased to a normal level (Chart 2). The jaundice persisted and, on April 15, there were 15 mg.% bilirubin. At operation, on April 17, a stone was found obstructing the common duct. The gall bladder was removed and the common duct drained. During the first 10 days postoperatively 2680 cc. bile drained from the common duct, and no bile was fed. The prothrombin fell

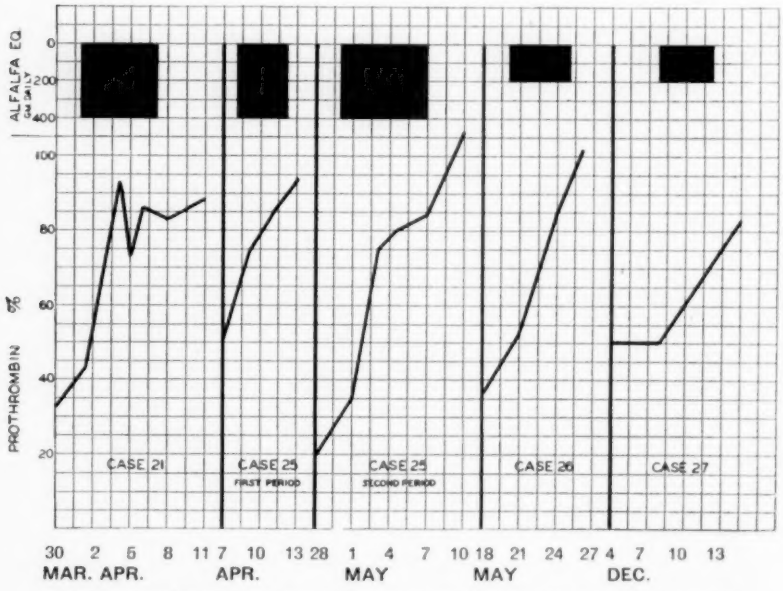

Chart 2.—Obstructive jaundice. Prothrombin response to alfalfa therapy.

gradually and at the end of this period it was 20% of normal. No spontaneous bleeding occurred, however, and the clotting time and Duke's bleeding time were not prolonged. Serum bilirubin on April 27 was 7.1 mg. Alfalfa extract, emulsified in sodium taurocholate solution, was then given, again with a rapid rise of the plasma prothrombin (Chart 2). Bile (200 to 400 cc. daily) continued to drain from the common duct; most of it was given back by mouth. During the last 18 days in the hospital, the prothrombin remained within normal limits and the jaundice subsided completely.

Case 26.—A white woman, aged 39, gave an indefinite history of epigastric distress and pain under the right costal margin for the past 6 years. During the past month a gradually increasing jaundice with acholic stools developed. On May 18, 1937, the van den Bergh test showed 29 mg. bilirubin. No bleeding tendency was present, although the prothrombin was at a rather low level. The prothrombin rapidly rose to a normal level

during a 6-day period of feeding alfalfa extract (equivalent of 200 gm. alfalfa meal in 30 cc. 2% sodium taurocholate daily), as shown in Chart 2. During this period of therapy the jaundice persisted, with 36 mg. serum bilirubin on May 22, and 24 mg. on May 24. During the following week there was partial spontaneous relief from the biliary obstruction, and no operative procedures were carried out.

Case 27.—A white woman, aged 27, had a severe attack of right upper abdominal pain 3 months ago. This was followed by dull pain which has persisted. Jaundice with acholic stools first was noted 6 weeks ago; this has also persisted. Van den Bergh test showed 17 mg. serum bilirubin on December 8, 1937. Clotting time and Duke's bleeding time were not prolonged. However, the plasma prothrombin was low. It was rapidly restored to a nearly normal level after feeding alfalfa extract (200 gm. equivalent alfalfa meal emulsified in 30 cc. 2% sodium taurocholate), as shown in Chart 2. At the end of this time, on December 11, there were 14 mg. serum bilirubin. The prothrombin remained at this high level throughout the patient's hospital course. Operation on December 22 revealed a stone, 2 cm. in diameter, in the ampulla, and several smaller stones in the common duct. The gall bladder was removed and the common duct drained.

The rapid rise in prothrombin obtained with bile and alfalfa feeding is quite in contrast to the very gradual rise seen with simple bile feeding in the biliary fistula case. It is to be noted that in Case 25 and Case 26 the prothrombin rose rapidly during periods of increasing jaundice. This indicates that the jaundice itself is not the essential factor in these cases.

We have had 2 patients with low prothrombin values which did not respond to alfalfa therapy. Both patients were deeply jaundiced, and in addition had evidence of extensive liver damage. Clinical impressions were a biliary cirrhosis of 3 years' duration in one case and a far-advanced malignancy involving liver in the other. The failure of these 2 cases to respond suggests that in addition to certain dietary essentials, a liver of good functional capacity is needed for the manufacture of prothrombin.

Comments. The data presented indicate that the bleeding tendency often seen in cases of obstructive jaundice and biliary fistula is due to a prothrombin deficit. Some patients fall within the danger zone and yet escape actual bleeding. Other factors, such as trauma, infection, operative hemorrhage, and exudate formation, are no doubt important in inciting actual hemorrhage. For this reason patients somewhat above the bleeding level must be considered as potential bleeders.

No doubt a variable degree of depression of liver function incident to obstructive jaundice is in part responsible for the lowering of the plasma prothrombin. We have shown[12,13] that toxic injury of the liver produces a profound fall in the prothrombin level. Liver injury probably is important in the very rapid fall in prothrombin seen in some cases of obstructive jaundice. The biliary fistula case cited, however, indicates that the absence of bile in the intestine is of major importance. This is in accord with the recent work of

Hawkins and Brinkhous,[6] in which they found that hypoprothrombinemia with a resultant bleeding tendency develops in dogs with chronic biliary fistula. In their experiments bile feeding prevented the fall in prothrombin. One might assume that the prothrombin deficit is due to difficulty in absorbing fat-soluble vitamins when bile is excluded from the gut. One could assume either that one of these vitamins serves as a building stone of prothrombin or that it was necessary to maintain normal function of the liver for the manufacture of prothrombin. McNealy, Shapiro, and Melnick[8] have presented clinical evidence that the bleeding tendency in obstructive jaundice is relieved by administration of viosterol along with bile salts. No prothrombin studies were made in their work, however.

Our data indicate that the prothrombin recovery period can be greatly shortened by feeding the fat-soluble extract of alfalfa meal along with bile. The extract used is obviously a mixture of many substances. It contains chlorophyll, carotene, and an undetermined amount of sterols, the latter no doubt activated to some extent by sunlight while the hay was being cured. It seems likely that the extract is a good source of most or all of the known fat-soluble vitamins, including large amounts of vitamin K.

Dam and Schønheyder[3] and Almquist and Stokstad[1] report a bleeding tendency in chicks which are maintained on a fat-free diet. The addition to the diet of fat-soluble extracts of alfalfa,[1] hog liver and certain other substances[2] was found to prevent the appearance of the disease. They believe that a new fat-soluble antihemorrhagic vitamin, vitamin K, is the factor concerned. Dam, Schønheyder and Tage-Hansen[4] and Quick[9] have presented data suggesting that a prothrombin deficit is the cause of the bleeding in this disease of chicks. Greaves and Schmidt[5] have recently found a hypoprothrombinemia in bile fistula rats similar to that reported by Hawkins and Brinkhous in dogs. Feeding of vitamin K cured the disease in their rats.

The evidence available suggests that the bleeding tendency seen in obstructive jaundice and biliary fistula is due at least in large part to a vitamin K deficiency. However, hemorrhagic disease due to a deficiency of this vitamin has not been produced in mammals by simple dietary means. For the present it seems best to accept the prothrombin deficit together with the beneficial effect of feeding bile and alfalfa, and to leave the more complete elucidation of the mechanism to further study.

Conclusions. The bleeding tendency so often seen in patients having obstructive jaundice or biliary fistulæ is due to a deficiency in plasma prothrombin. This deficiency is related in part at least to absence of bile in the intestine and is relieved by bile feeding. The beneficial effect of bile feeding is greatly enhanced by supplementing the bile with fat-soluble alfalfa extract, rich in vitamin K.

This work was made possible through the generous coöperation of many members of the Departments of Internal Medicine and Surgery. We are especially indebted to Dr. Frank R. Peterson.

For a preliminary report of this work see Proc. Soc. Exp. Biol. and Med., **37**, 628, 1938.

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COMBINED SYSTEM DISEASE WITHOUT OBVIOUS EVIDENCE OF PERNICIOUS (MACROCYTIC) ANEMIA.

Report of 8 Cases; 1 Autopsy.

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Since the publication of the article by Russel, Batten and Collier in 1900,[10] it has been known that degenerative changes in the spinal cord (subacute combined degeneration of the spinal cord) may accompany pernicious anemia. The combination is so frequent that for many years the diagnosis of pernicious anemia has been almost immediately presumed in a patient with signs and symptoms referable to the posterior and lateral tracts of the spinal cord. This presumption assumed more weight when it was recognized that such symptoms and signs may develop in patients many years before the appearance of anemia.[6, 9]

In the last decade, however, a considerable number of cases of subacute combined degeneration of the spinal cord have been reported in patients without significant anemia.[1, 8, 7, 8] When compared with the number of cases with definite evidences of pernicious anemia, such cases are uncommon. Necropsy reports of cases without pernicious anemia are rare and doubts have been cast on the validity of many of the reported cases.[15]

The classical triad of pernicious anemia is: a hyperchromic anemia, degenerative changes in the spinal cord and a defective

gastric secretion (achylia gastrica and an absence of the intrinsic factor of Castle). The exact relationship of these three factors[2,8,13,14] is not known, since the changes in the spinal cord, as stated previously, and the disturbance of the gastric function may precede the blood changes by many years.[9] It is possible that the degenerative changes in the spinal cord may be related to some as yet unknown factor, independent of the blood changes and the achylia gastrica; as yet the nature of such an unknown factor can be only conjectured. A defect in the absorption of vitamin B is suggested by the fact that most of the reported cases have associated with the conditions which might be accompanied by such a defect.[11a,b,15] We, therefore, thought it desirable to report this study of 8 cases of subacute combined degeneration of the spinal cord without a macrocytic anemia.

A few words are necessary regarding the methods of diagnosis in these cases reported. Many diseases of the nervous system may produce changes in the posterior and lateral tracts of the spinal cord with a resulting symptomatology closely resembling that of subacute combined degeneration of the cord as seen in pernicious anemia. Only a few of the more common ones need be mentioned, such as multiple sclerosis, syphilitic meningomyelitis, syringomyelia and spinal cord tumors. To exclude as far as possible the above mentioned diseases as well as pernicious anemia and other conditions, the following tests were made on all of our patients: careful anamnesis, physical and neurologic examination, a thorough study of the blood, gastric analysis after test meals or histamine, lumbar puncture, Roentgen ray of the spine and serologic tests on the blood and cerebrospinal fluid. For convenience of presentation the cases are divided into four groups: 1, cases without evidence of a disturbance of blood formation and with normal gastric acidity; 2, a case without evidence of disturbance of blood formation but with achylia gastrica; 3, cases with hypochromic (secondary) anemia and normal gastric acidity; and, 4, a case with hypochromic (secondary) anemia and achylia gastrica.

Group 1.—*Cases Without Evidence of a Disturbance of Blood Formation and With Normal Gastric Acidity:*

Case 1.—Patient M. N. (Hosp. No. 828713), a 47-year-old female, was admitted to the hospital on July 18, 1936, complaining of weakness of legs, staggering gait and numbness of fingers and hands of several months' duration. For 4 months the symptom complex had become progressively worse and she had fallen 3 times. No history of dietary inadequacy could be obtained.

The patient was obese and well developed. The tongue was smooth at the edges. There was marked weakness of the legs and a slight weakness of the arms, particularly the right. The muscles were well developed and there was no evidence of atrophy. There was hypesthesia to touch and pin prick in the right leg and in the right hand. The sense of vibration was lost in the right tibia and diminished in the left. Position sense was impaired in the toes. The deep reflexes in the arms and knees were exaggerated but the ankle jerks were absent. The Romberg test was positive. Stimulation of

the plantar surface of the feet produced a typical Babinski sign on the right and an equivocal response on the left foot. The abdominal reflexes were absent. On two occasions, the hemoglobin content of the blood was 78% (Sahli). The red blood count was 4,230,000 and 4,460,000 per c.mm.; the white blood count was 6100 per c.mm. with a normal differential count. The Hinton test on the serum was negative. Analysis of the gastric juice after a test meal of 50 cc. of 10% alcohol showed 10 degrees of free acidity and 18 of total acidity. The urine was normal. The cerebrospinal fluid was under a pressure of 175 mm. and the response to compression of the jugular veins was normal. The fluid contained 2 white cells per c.mm. The globulin test was negative and the protein content was 44 mg. per 100 cc. The colloidal gold and Wassermann tests on the fluid were negative.

The patient was treated daily with intramuscular injection of 10 cc. liver extract equivalent to 50 gm. of whole liver. After 10 injections, she was able to get out of her bed and walk around the ward. There was a marked increase of the muscular strength of the legs and diminution in the areas of hypesthesia. There was no improvement in the vibration or position senses. The patient was discharged 3 weeks after entry with instructions to return to the outpatient department for further treatment. After 2 injections were given the patient lapsed from treatment until almost a year later when she was readmitted to the hospital for reëxamination at our request. In the meantime, she had received no treatment and had carried on her routine household duties as usual. On the second admission on July 17, 1937, the neurologic findings were much the same as they were on discharge 1 year previously. The hemoglobin content of the blood was 80% (Sahli) and the red blood count 4,230,000 per c.mm. The gastric content, removed 20 minutes after the injection of histamine, showed 40 degrees of free acid. A second lumbar puncture gave entirely normal findings.

Case 2.—Patient C. A. (Hosp. No. 839775), a 63-year-old married woman, was admitted to the hospital on January 20, 1936, complaining of numbness, tingling in the feet, "cramps," numbness of the legs and difficulty in walking, of 3 weeks' duration. She had fallen several times and had been bedridden for a week previous to her hospitalization. For the preceding 6 months, there was urinary urgency, 10 times in the day and 6 to 8 times at night.

Upon examination, it was found that her tongue was smooth and beefy red, that there were numerous discrete, moderately tender enlarged lymph glands of various size in the cervical, axillary and inguinal regions. One of the glands, removed at biopsy, was regarded as showing evidence of Hodgkin's disease. There was a mild degree of arteriosclerosis of the retinal vessels. The muscles of the legs were weak and the heel-shin test was performed with difficulty. The vibration sense was absent below the level of the crest of ilium. Position sense was impaired in the toes and ankles. The deep reflexes were present in the arms but the knee- and ankle jerks were absent. Stimulation of the plantar surface of the feet produced an atypical Babinski response on the right and a normal response on the left. Examination of the blood on 4 occasions showed a hemoglobin content of 80% (Sahli), a red count varying from 4,020,000 to 4,340,000 per c.mm. and a white count from 6400 to 7300 per c.mm. with a normal differential count. The mean corpuscular volume of the red cells was 90.3% and the hematocrit content was 39.2%. The icteric index was 5.0 and the Hinton test on the serum was negative. Analysis of the gastric content showed 20 degrees of free acidity after 100 cc. of 7% alcohol by mouth. The urine contained many white blood cells. Roentgen rays of the spine were normal. The cerebrospinal fluid was under a pressure of 140 mm. and the response to jugular compression was normal. The fluid was clear and colorless and contained no cells. The protein content was 31 mg. per 100 cc. The colloidal gold and Wassermann tests on the fluid were negative. The findings of a

second lumbar puncture were the same as those of the previous puncture excepting the protein content, which was 50 mg. per 100 cc.

For 5 days, the patient was treated daily by intramuscular injection of 10 cc. of liver extract, equivalent to 50 gm. of whole liver and on the 6th day was started on a series of deep Roentgen ray therapy (20 exposures). On her discharge 2 months after admission, patient was greatly improved physically. There was a gradual diminution of the size of the enlarged glands but no change was noted in the reflexes, vibration or position senses.

Case 3.—Patient M. A. Y. (Hosp. No. 842619), a 65-year-old married woman, was admitted to the neurologic service on December 23, 1936, complaining of chronic constipation and numbness and tingling of fingers and toes of 2 years' duration. She was well developed and well nourished. There was no atrophy of the papillæ of the tongue. The heart was enlarged and there was a moderate degree of sclerosis of the peripheral and retinal vessels. There was a spastic weakness of the muscles of the extremities without any atrophy. The finger-nose and heel-shin tests were poorly performed. Vibration sense was impaired in both legs and absent in the left ankle. The deep reflexes were all greatly exaggerated with bilateral ankle clonus, Hoffmann and Babinski signs. The abdominal reflexes were absent. The results of the examination of the blood on 4 occasions during her stay in the hospital were as follows: the hemoglobin content varied from 80 to 83% (Sahli), the red cell count from 3,890,000 to 4,100,000 per c.mm. with a slight degree of achromia. The mean corpuscular volume was 88%, the hematocrit content 44%, the white blood count 13,000 per c.mm. with a differential count of neutrophils 75%, lymphocytes 19, large mononuclears 4, basophils 1 and eosinophils 1%. Analysis of the gastric contents showed 98 degrees of free hydrochloric acid 30 minutes after 1 mg. of histamine injection. A second gastric analysis showed 17 degrees of free acid in the fasting specimen and 97 degrees in the specimen removed 30 minutes after the injection of histamine. The Hinton test on the serum was negative. Lumbar puncture was performed on 2 occasions. The cerebrospinal fluid was under a normal pressure and the response to jugular compression was normal. The fluids were clear and colorless, contained no cells and had a protein content of 26 and 38 mg. per 100 cc. Colloidal gold and Wassermann tests were negative.

Ten cubic centimeters of liver extract equivalent to 50 gm. of whole liver were given intramuscularly every day for 2 weeks. Under this régime the patient rapidly improved. She was able to get about the ward at the end of the second week, and was discharged 4 weeks after entry very much improved.

Comment. The 3 above cases present the typical neurologic syndrome commonly associated with pernicious anemia. There were paresthesia in the hands and feet, weakness and ataxia of the extremities and physical signs of involvement of the posterior and lateral tracts of the spinal cord. In none of the 3, however, was there any significant disturbance of the blood formation or achylia gastrica.

In Case 1 there was no associated disease which could explain the symptoms and signs. In the second case, the possibility of any involvement of the spinal cord by the Hodgkin's disease must be considered.[3,5] No evidence in support of this hypothesis could be obtained. There was no evidence of cord compression on neurologic examination, lumbar puncture or Roentgen ray of the spine.

The age of the third patient (65 years) and the condition of the peripheral and retinal vessels suggest that arteriosclerosis may have played some rôle in the production of the signs and symptoms.

The degree of improvement in Cases 1 and 3 following parenteral treatment with liver extract merits attention.

Group 2. *A Case Without Evidence of a Disturbance of Blood Formation but With Achylia Gastrica.*

CASE 4.—Patient M. O. N. (Hosp. No. 801517), a married woman, aged 74, was admitted on October 12, 1935, complaining of weakness of legs of 9 months' duration. Her symptom complex became progressively worse, so that in a short time she began to drag her legs and had to keep her eyes on her feet while walking. For 2 weeks before admission she developed spasmodic radiating pains from the thighs downward.

The patient was well developed and moderately obese. The blood pressure was 140/80. Roentgen ray of the spine showed hypertrophic arthritis in the lumbar region. The important positive neurologic findings were: weakness of the legs and toes; absent knee- and ankle jerks; bilateral Babinski signs; hypesthesia below the knees and absence of vibration sense from the clavicles. There was no significant smoothing of the tongue.

The hemoglobin content of the blood was 90% (Sahli), and the red blood count was 4,500,000 per c.mm. The red cells were normal in size and shape. The white blood count was 6550 per c.mm. with a normal differential count. The cell volume was 4.05, hematocrit content 43.74, mean corpuscular volume 96.9 and mean corpuscular hemoglobin content 31.9. The serum Kahn test was repeatedly negative. The urine was normal and the serum non-protein nitrogen was 32 mg. per 100 cc. There was no free acid in the gastric content either before or after the injection of 1 mg. of histamine. The pressure of the cerebrospinal fluid and its response to compression of the jugular veins were normal. The fluid contained 45 mg. of protein per 100 cc. and the colloidal gold and Wassermann tests were negative.

The patient was not treated during her stay in the hospital.

Comment. In this patient, there were outstanding signs of involvement of both posterior and lateral tracts of the spinal cord. There was an achylia gastrica but the blood picture was within the normal limits. The age of the patient (74 years) suggests that arteriosclerosis may have played some rôle in the production of the symptoms and signs.

Group 3. *Cases With Hypochromic (Secondary) Anemia and Normal Gastric Acidity.*

CASE 5.—Patient H. C. (Hosp. No. 804254), a 67-year-old hotel clerk, entered the hospital on November 7, 1935, with complaints of increasing weakness of legs and difficulty in walking for 9 months' duration. He had some urinary urgency and occasional fecal incontinence for a year or 2 before admission.

Examination showed a rather obese, elderly looking person with marked general weakness, slight sclerosis of the retinal vessels and slightly smoothed papillæ of the tongue. The blood pressure was 140/90. There was ataxia and asynergia of the lower extremities. Vibration and position senses were markedly impaired in the legs. The knee jerks were normally active but the ankle jerks were absent. There was a bilateral Babinski response. The abdominal and cremasteric reflexes were absent. The Romberg test was positive. The blood was examined 9 times during the patient's stay in the hospital. The hemoglobin varied between 76 and 80% (Sahli); the red

count between 3,700,000 and 3,800,000 per c.mm.; the white count between 7550 and 14,000 per c.mm. The differential counts were within normal limits. The hematocrit content was 36.9; the mean corpuscular hemoglobin content 33.8; the mean corpuscular hemoglobin volume 85.6, and the icteric index 3.0. The Hinton test of the serum was negative. Lumbar puncture showed normal findings except for a protein content of 61 mg. per 100 cc. on fluid removed at first puncture and 102 mg. per 100 cc. on that removed 10 days later. The cerebrospinal fluid Wassermann reaction was negative. Gastric analysis before liver treatment showed 12 degrees of free acid and 22 of combined acid in the fasting specimen. Thirty minutes after subcutaneous injection of 1 mg. of histamine there were 96 degrees of free acid and 13 degrees of combined acid. Examinations of the urine were normal. Roentgen ray of the spine showed hypertrophic arthritis in dorsolumbar region.

Fairly intensive treatment by intramuscular injections of liver extract was given to the patient. Two weeks later, he was able to get up and to walk about the ward. At the same time, physiotherapy in form of heat, massage and passive motion was also given to the legs. At the time of discharge on January 16, 1936, patient was greatly improved. Intramuscular injections were continued once a week in the outpatient department and the patient continued to improve slightly until October, 1936, when he was admitted to the hospital on account of symptoms of coronary thrombosis, and died. Unfortunately, the spinal cord was not removed at autopsy.

Case 6.—Patient B. D. (Hosp. No. 770716), a 46-year-old married negress, was admitted to the hospital on November 10, 1933, complaining of numbness of the hands for 5 years' duration. The symptoms started in the right hand and extended to the left hand after 2 years accompanied by dragging of the left leg. The symptoms became progressively worse so that at the time of her admission, she had great difficulty in executing fine movements of her fingers. One month before her admission, her hands became icy cold. The diet as given by the patient seemed to be well balanced and adequate.

On physical examination there was bilateral interstitial keratitis, slightly saddle-shaped nose, peg-shaped lateral incisors and dystrophic lower teeth. The blood pressure was 135/98. The abnormal findings on neurologic examination were: bilateral deafness of middle ear type; spasticity and weakness of the legs; hyperactive tendon reflexes except for the ankle jerks, which were absent; bilateral Babinski and Hoffmann signs; absent abdominal reflexes; difficulty in recognizing objects with the tips of the fingers; impaired position and vibration sense in the legs. The blood hemoglobin content was 74% (Sahli). The red blood count was 3,550,000 per c.mm. The mean corpuscular hemoglobin content 30.9; mean corpuscular volume 105; icteric index 4.0. The white blood count was 6000 with the differential count as follows: neutrophils 58%; small lymphocytes 17; large lymphocytes 15; large mononuclears 7; eosinophils 1; stippled and undifferentiated forms 2%. Gastric analysis showed 22 degrees of free acid and 33 of combined acid in the fasting specimen. The cerebrospinal fluid was under a pressure of 110 mm. The dynamics were normal. The protein content was 32 mg. per 100 cc. and the colloidal gold reaction was negative. Repeated Wassermann reaction of both blood and cerebrospinal fluid was negative. The urine was normal. Patient left the hospital before treatment could be instituted.

Case 7.—Patient E. B. K. (Hosp. No. 665464), a married woman aged 37, was admitted to the Neurological Service, Boston City Hospital, on March 11, 1932, because of sudden attacks of crying spells during which time she was confused, irrational, overtalkative, combative, unable to recognize her husband and expressed delusion of persecution. She had 3 similar

attacks in the 2 months before admission. For 3 years before admission, patient had been having melena and losing weight. For 1 year before admission, she suffered from blood in stools and was treated for intestinal worms.

On examination, the patient was greatly emaciated and appeared anemic. The tongue was smooth and red in color. All deep reflexes were greatly exaggerated with bilateral ankle clonus, Babinski and Hoffmann signs. The sensory examination was not entirely satisfactory due to the lack of coöperation. However, the vibration sense seemed to be definitely impaired over the legs and the lower lumbar spine.

The blood hemoglobin content was 48% (Sahli), the red blood count 2,800,000 per c.mm. and the white blood count 13,000 per c.mm. Throughout her 10-month stay in the hospital, the patient's blood was examined at frequent intervals. The blood hemoglobin remained at the level of 40 to 52% (Sahli) with no significant changes in the total red or the differential count. However, there was a considerable variation of the total white blood count ranging from 4100 to 17,750 per c.mm. The red blood cells appeared normal in shape but showed marked achromia and some variation in size. The serum non-protein nitrogen was 46 mg. and the serum sugar content was 100 mg. per 100 cc. The serum Kahn, Hinton and Wassermann reactions were negative. Gastric analysis on admission showed 33 degrees of free acid and 54 of total acid in the fasting specimen. Four days later, there were 55 degrees of free acid and 90 of total acid in the fasting specimen. Throughout her stay in the service, patient ran a septic temperature varying from 96° to 103° F. Repeated blood cultures were negative. Roentgen ray of the chest and the gastro-intestinal tract showed no significant abnormalities. The electrocardiogram was normal. Frequent examination of the urine showed numerous white cells, singly and in clumps. The cerebrospinal fluid was examined on 2 occasions. It was under a normal pressure and the response to compression of the jugular veins was normal. The fluid was clear and colorless and contained no cells. The total protein content was 17 mg. and 23 mg. per 100 cc. and the colloidal gold reactions were 1233211000 and 1111100000. Wassermann reactions were negative. Repeated agglutination tests of the serum with typhoid and paratyphoid organisms were negative.

For the first few days after admission, patient was irrational, overtalkative, emotionally labile, striking at nurses and attendants, spitting on the walls and refusing to take food. She expressed a fear that someone might do harm to her.

The patient remained in the hospital for 10 months and was treated daily for 1 week with intramuscular injections of 10 cc. of liver extract representing 50 gm. of whole liver, together with 4 gm. of vegex 3 times daily and a high caloric, high vitamin diet. There was no change in the general clinical picture, neurologic signs or blood content on this régime nor after transfusion of 500 cc. of citrated blood. A severe degree of cystitis developed which did not respond to forcing fluids, urotropin and bladder irrigation. The patient continued to be noisy and difficult to manage. Frequent elevation of temperature continued and patient died on January 15, 1933, in an extreme degree of emaciation.

Autopsy was performed 4 hours postmortem. The body was that of a very poorly developed and extremely emaciated female adult. The lower lobe of the left lung showed moderate increase of consistence and decrease in crepitation. The loops of ileum were bound together by thin firm fibrous adhesions as the liver and spleen were adherent to the diaphragm. The wall of the sigmoid and rectum was greatly thickened and the muscularis stood out as a translucent milky white. The muscosa was thickened, firm, injected, and furrowed with longitudinal ulcers in a few irregular areas.

Urinary bladder was slightly injected. Kidneys and ureters were negative. There were slight atheromatous changes in the aorta. The spinal cord appeared grossly normal. Sections of the cord stained by the Weigert Pal method showed a moderate degree of degeneration of the myelin in the posterior columns and around the periphery of the cord in the lateral and anterior columns. In the region of the crossed pyramidal tracts, however, there was a marked loss of the myelin.

Comment. Signs and symptoms of involvement of the posterior and lateral tracts of the spinal cord were pronounced in all of these cases. The anemia in Case 5, which was only of a slight degree, was definitely of the hypochromic (secondary) type and the patient responded remarkably well to the liver treatment. In Case 6, there was slight variation in the size and shape of the red blood cells. However, the combination of a normal diet and normal gastric acidity in a negress was considered by medical consultants as making the diagnosis of pernicious anemia extremely unlikely. On the other hand, the saddle nose, the interstitial keratitis and the dystrophic lower teeth, suggested the diagnosis of congenital syphilis. The possibility that the signs and symptoms of spinal cord disease could be explained on this basis was not definitely excluded by the normal spinal fluid and negative blood serology.

In Case 7, there was a marked degree of hypochromic anemia secondary to an ulcerative colitis. The signs and symptoms in the nervous system in this case could readily be attributed to an impairment of the function of the gastro-intestinal tract, with inadequate absorption.

Group 4. *A Case With Hypochromic (Secondary) Anemia and Achylia Gastrica.*

Case 8.—Patient A. M. B. (Hosp. No. 773232), a married white female aged 45, was admitted on January 14, 1935, complaining of difficulty in walking and a sensation of unsteadiness following a fall in the snow at age of 35. For the past 8 years, she had to walk with the aid of a cane or other support and had gained an unknown amount of weight. The right leg was at the same time growing fatter than the left. During the past 2 years, absence of menstrual flow had alternated with periods of menorrhagia.

On examination, the patient was obese and appeared anemic. The fat was distributed in the form of flabby pads on the trunk and extremities tending to spare the face, hands and feet. The right foreleg was particularly large and was rendered shapeless by the pads of fat which were tender on pressure. The tongue was smooth. The positive neurologic findings were: weakness of the legs, impaired position and vibration sense in the legs, hyperactive tendon reflexes throughout with bilateral Babinski and Hoffmann signs, the finger-to-moving object test was very inaccurately done but the finger-nose test was fairly well performed. Gastric analysis showed no free acidity in the fasting specimen or in the specimen removed after the ingestion of 100 cc. of 10% alcohol by mouth or after the intramuscular injection of 1 mg. of histamine. The combined acidity was 13, 29 and 4 degrees in the 3 specimens respectively. The blood hemoglobin was 56% (Sahli), the red blood count 4,600,000 per c.mm. and the white blood count 4800 per c.mm. The differential count of the blood was within normal limits. The hemotocrit content was 33.1, mean corpuscular hemoglobin

content 26.4, mean corpuscular volume 60.2 and icteric index 2.0. With the institution of liver and iron therapy, the blood hemoglobin rapidly rose to 65% (Sahli) and the red blood count to 5,500,000 per c.mm. The cerebrospinal pressure was normal and the total protein content in the cerebrospinal fluid was 36 mg. per 100 cc. The cerebrospinal fluid Wassermann and the serum Hinton tests were negative. Daily injections of liver extract were given intramuscularly (10 cc. of liver extract representing 50 gm. of whole liver) together with iron administration in the form of Feosol and high vitamin diet, patient was discharged after 5 weeks in the hospital, her neurologic condition apparently not affected by the above treatment.

Comment. In this patient, in addition to a mild degree of hypochromic anemia and achylia gastrica, there were evidences of endocrine dysfunction. The distribution of the fat and its tenderness on pressure were characteristic of the so-called syndrome of adiposa dolorosa.

General Comment. In summarizing our cases, it is noteworthy that 7 of the 8 patients were women. The ages varied between 37 and 74 years, divided according to decades as follows: fourth, 1; fifth, 3; seventh, 3; and eighth, 1.

Weakness and ataxia of the legs were the most common symptoms and were present in all of the 8 cases. Paresthesia (numbness and tingling) of the extremities were present in 5 and bladder symptoms in 2.

In the general physical examination, evidence of arteriosclerosis were present in 3 patients, all of whom were in the seventh decade. In the neurologic examination, the ankle jerks were absent in 5 patients, hyperactive in 2 and normal in 1. The knee jerks were absent in 2, hyperactive in 4 and normal in 2 patients. In all of the 8 patients, the plantar responses were of Babinski type and the vibration and position senses were impaired in the lower extremities. A definite loss of cutaneous sensibility was found in only 2 patients.

Roentgen rays of the spine were normal in 6 patients and there was a moderate degree of hypertrophic arthritis in 2. The serologic tests were negative in the blood and cerebrospinal fluid in all 8 patients. The cerebrospinal fluid was under a normal pressure and the response to compression of the jugular veins was normal in all. The only abnormality in the fluid was a slight increase in the protein content in Cases 2 and 5.

Complication factors were present as follows: Arteriosclerosis in Cases 2, 3 and 5; Hodgkin's disease in Case 2; ulcerative colitis and diarrhea in Case 7; glandular dysfunction in Case 8 (? adiposa dolorosa).

Liver extract* was given parenterally to 6 of the 8 patients (Cases 1, 2, 3, 5, 7 and 8). Good subjective response as manifested by improvement of strength was obtained in 4 of the 6 patients,

* The extract was prepared in the Thorndike Memorial Laboratories by the method of Strauss, Castle and Taylor.

and in none of the cases treated with liver was there a progression of the neurologic symptoms. These results are in harmony with those obtained by Strauss and his co-workers[12] in patients with combined system disease associated with pernicious anemia.

Discussion. Our cases were analyzed in detail to determine if any factor common to them all could be found. No such factor was found. The most significant facts were that 7 of the 8 patients were women and 4 of the 6 patients who were treated with liver extract were remarkably improved. Hypochromic anemia of a moderate degree was present in 4 patients and achylia gastrica in one of these 4 and in 1 additional patient.

The existence of a common factor in cases with signs and symptoms of subacute combined degeneration of the spinal cord without pernicious anemia can, as said before, only be postulated. Since impaired utilization of vitamin B is the most plausible explanation of the spinal cord symptoms in patients with pernicious anemia and it is probable that the same factor is responsible for the occurrence of such symptoms and signs in patients here reported. The evidence presented here, particularly the response to liver therapy, is suggestive but not sufficient to be conclusive evidence for this hypothesis and it is possible that this type of spinal cord disease is only symptomatic of various disease conditions.

Summary. 1. Eight patients with subacute combined degeneration of the spinal cord are reported. In 4 of them there was no evidence of a disturbance of blood formation and in 4 there was a moderate degree of hypochromic (secondary) anemia. Achylia gastrica was found in 1 of the patients in both of the above groups.

2. Among the complication factors were arteriosclerosis in 3 cases, Hodgkin's disease, ulcerative colitis and glandular dysfunction.

3. A good response to parenteral liver therapy was obtained in 4 of the 6 patients so treated.

4. The etiology of subacute combined degeneration without the so-called "pernicious anemia" is briefly discussed.

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THE SIZE OF THE RED BLOOD CORPUSCLE IN DIABETES MELLITUS.

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In 1931 Root[15a] reviewed 48 cases of associated diabetes mellitus and pernicious anemia; again, in 1933, he[15b] reviewed 31 additional cases. He believes there is an increase in the association of the two diseases and attributes this to the prolongation of life in both diabetes and pernicious anemia as a result of the discovery of insulin and liver therapy. In these reported cases, Root omitted those which failed to fulfill the criteria for a definite diagnosis of pernicious anemia, namely: (1) macrocytic anemia or symptoms of spinal cord degeneration or both; (2) achlorhydria; (3) bilirubinemia; (4) reticulocyte response to adequate doses of liver.

It is a well known fact that diabetes mellitus may cause symptoms quite similar to those found in pernicious anemia. Glossitis and numbness and tingling of the hands and feet are fairly common in diabetes. Achlorhydria was found by Joslin,[11] and Bowen and Aaron[1] to be present in 30 to 40% of diabetics and its frequency increased with the age of the patient and the duration of the disease. Anemia, although an uncommon finding in uncomplicated diabetes, may be present and is quite frequent in complicated diabetes.

Root[15a] states that a large group of borderline cases seen at the Deaconess Hospital were not included in the published cases. In this group of borderline patients, some of the criteria for the diagnosis of pernicious anemia were absent.

Because this type of case was seen rather frequently, and because at times there was some difficulty in diagnosing pernicious anemia in combination with diabetes, it was decided to study the blood of diabetics by means of corpuscular volume. On reviewing the literature, it was found that no such study of the blood had been undertaken in cases of uncomplicated diabetes. Several papers have discussed the changes in the volume of the red blood cell in diabetic coma but most of them are incomplete: in some, no mention is made of the method used to determine the corpuscular volume; and in others the number of cases cited is too small to be of value in drawing conclusions.

It is the opinion of Holler and Kudelka,[10] Foldes,[4] Detre,[2] and Hashimoto[8] that in diabetic coma the mean volume of the red blood cell is increased and the diameter of the cell is decreased. Detre states that the volume of the red blood cell is increased in proportion to the degree of acidosis, the maximum volume being reached in coma. Holler and Kudelka, likewise, think that the degree of acido-

sis determines the volume of the erythrocyte. They also believe that if carbon dioxide is passed through a sample of the blood, the diameter of the red blood cells becomes smaller and the cell becomes more spherical in shape.

None of the above mentioned authors states what specific substance in the blood stream during acidosis causes this change. One is led to believe from their discussions that an increase in acidity of the blood causes the changes in the erythrocytes.

Method. All diabetic patients admitted between March 10, 1935, and April 10, 1935, to the New England Deaconess Hospital and George F. Baker Clinic, who were on the service of Dr. Joslin, were considered for this study. The blood determinations which will be described later were made solely on patients who were found, on routine history, physical examination and laboratory work, to be free of any associated disease or any complication of diabetes other than diabetic acidosis or diabetic dwarfism. The 49 selected patients are grouped in Tables 1, 2 and 3; 15 additional cases of diabetic acidosis are grouped in Table 2A. These cases were admitted to the Metabolic Ward of Johns Hopkins Hospital.*

The routine followed in the study of the blood in all of these cases at the Deaconess Hospital is as follows: red blood cell counts, hemoglobin and hematocrit determinations. Urine which was voided not more than 2 hours before or after the blood specimen was taken, was tested for diacetic acid and acetone. The carbon dioxide combining power was determined in any case suspected of having acidosis. Blood-sugar values were determined in 30 uncomplicated diabetics, and all cases of diabetic acidosis and diabetic dwarfism. Venous blood was used for blood studies, 5 cc. being collected in an absolutely dry syringe and put into a small bottle which contained 6 mg. of ammonium oxalate and 4 mg. of potassium oxalate.[9] Two or more red blood-cell counts were made on each specimen of blood. No figures were used for red cell counts unless they checked within 100,000, in consecutive counts. The average of the counts which checked is the figure used to represent the red blood cell count of that specimen. The hematocrit determinations were made with the Wintrobe[16a,b] hematocrit, according to his specifications. The centrifuge used was a large electric type which would spin at about 4500 revolutions per minute. The centrifuge was run at its full speed, and checked several times during the study to be sure that packing of the red blood cells was complete. Hemoglobin determinations were made on a Dubosecq colorimeter, a Newcomer disk being used for the standard.

There are sixty-four cases in this study and they are presented in three groups: Table 1—uncomplicated diabetes; Tables 2 and 2A—diabetic acidosis; and Table 3—diabetic dwarfs. In each table the cases are arranged in the order of decreasing corpuscular volumes.

Results. 1. Of 42 cases of uncomplicated diabetes mellitus (Table 1) 6 (14.3%) have a corpuscular volume of 95 cu.μ, or over; 11 (26.1%) have a corpuscular volume of 93 cu.μ, or over.

2. Tables 2 and 2A are composed of 18 cases of diabetic acidosis. The 3 cases in Table 2 are children; the 15 in Table 2A are adolescents and adults. Two of the children were found to have corpus-

* I am greatly indebted to Dr. J. E. Howard, who gave me the data on some of these patients.

cular volumes of 84 cu.μ and 85 cu.μ, respectively; 1 was found to have a corpuscular volume of 75 cu.μ. Each of these children had marked diabetic acidosis.

TABLE 1.—UNCOMPLICATED DIABETICS.

Case No.	R.B.C., millions/c.mm.	Hbg., gm./1000 cc.	Volume packed R.B.C., cc./100 cc.	Corpuscular volume, cubic microns.	Corpuscular hbg., micro micrograms.	Mean corpuscular hbg., conc., %.	Mean cell diameter, microns.	Mean cell thickness, microns.	Blood sugar, mg. %	Diacetic acid and acetone urine.	Age.	Sex.
1	4.45	15.3	42.0	96	35	36	..	..	290	0	25	F
3 D	4.43	15.3	42.0	95	35	36	..	..	..	0		
4 W	3.81	..	39.0	102	..	..	7.12	2.56	..	0		
5 W	4.59	..	39.0	85	..	..	..	..	..	0		
2	4.58	14.8	45.1	99	32	33	..	..	220	0	73	M
24 H	4.43	14.2	41.3	93	32	35	..	..	..	0		
3	5.67	19.5	55.8	98	34	35	..	..	..	0	57	M
3 W	5.20	14.2	49.2	95	27	29	..	..	..	0		
3 W, 1 D	5.20	..	49.0	94	..	..	7.64	2.08	..	0		
4	4.32	12.5	41.5	96	29	30	..	..	80	0	36	F
5	4.93	15.8	46.5	94	32	34	..	..	90	0	58	M
24 H	4.95	15.3	47.0	95	31	33	..	..	..	0		
6	5.27	15.8	50.1	95	30	32	..	..	160	0	49	M
24 H	5.42	16.2	48.5	90	30	32	..	..	150	0		
7	4.03	11.0	38.0	94	29	29	..	..	120	0	71	M
8	4.91	15.8	46.0	94	32	34	..	..	90	0	53	M
9	4.43	14.2	41.0	93	32	35	..	..	120	0	39	F
10	4.49	14.5	41.7	93	32	35	..	..	110	0	28	M
11	4.82	15.6	45.0	93	32	35	..	..	..	0	..	F
12	4.99	14.2	45.7	92	29	31	..	..	..	0	48	F
13	5.02	15.3	45.9	92	31	33	..	..	110	0	55	F
14	4.73	15.8	43.4	92	33	36	..	..	240	0	56	M
15	5.22	14.9	47.6	91	29	31	..	..	180	0	41	F
16	4.73	15.3	43.2	91	32	35	..	..	170	0	52	M
17	4.76	15.9	43.5	91	33	37	..	..	160	0	80	M
18	4.96	14.2	44.6	90	29	32	..	..	260	0	29	F
19	5.34	16.1	48.0	90	30	34	..	..	..	0	48	F
24 H	5.36	16.2	48.5	90	30	33	..	..	..	0		
20	3.99	12.2	36.0	90	31	34	..	..	200	0	56	F
21	4.27	11.9	38.1	89	28	31	..	..	..	0	..	F
22	4.77	13.6	42.0	88	29	32	..	..	180	0	41	M
23	4.46	11.3	39.0	88	25	29	..	..	270	0	24	F
24	4.96	14.0	43.4	88	29	33	..	..	..	..	..	F
25	5.54	15.3	48.3	87	28	32	..	..	240	0	38	M
26	5.41	15.6	46.4	86	29	34	..	..	230	0	55	F
24 H	5.55	16.0	46.8	84	29	34						
27	5.04	14.4	43.1	86	29	33	..	..	220	0	57	F
28	5.08	15.6	43.5	86	31	36	..	..	170	0	27	M
29	4.61	13.8	39.2	86	30	35	..	..	222	+	34	F
30	4.72	13.0	40.0	85	28	33						
31	4.80	14.8	40.6	85	31	36	..	..	150	0	60	M
32	5.63	15.8	47.0	84	28	34	..	..	80	0	19	M
33	4.74	15.3	39.8	84	32	38	..	..	270	0	75	F
34	4.92	14.9	41.5	84	30	36	..	..	..	0	42	M
35	4.95	13.8	41.2	83	28	34	..	..	..	0	43	M
36	5.29	15.0	44.0	83	25	34	..	..	..	0	30	M
37	5.43	15.2	45.0	83	28	34	..	..	..	0	29	M
38	5.77	17.4	48.0	83	30	36	..	..	140	0	18	M
39	5.46	15.6	44.5	82	29	35	..	..	290	0	23	F
40	5.27	14.7	43.2	82	28	34	..	..	..	0	39	F
41	6.17	18.0	50.0	81	29	35	..	..	110	0	26	M
42	5.49	15.4	43.5	79	28	35	..	..	220	0	19	M

H = Hours; D = Days; W = Weeks; M = Months.

Of the 15 cases in Table 2A, 7 (46.6%) were found to have a corpuscular volume of 95 cu.μ, or over, and 11 (73.3%) were found to have a corpuscular volume of 93 cu.μ. or over, at the time of acidosis. If, however, we consider each readmission of Cases 55 and

TABLE 2.—DIABETIC ACIDOSIS (CHILDREN).

Case No.	R.B.C., millions/c.mm.	Hbg., gm./1000 cc.	Volume packed R.B.C., cc/100 cc.	Corpuscular volume, cubic microns.	Corpuscular hbg., micro micrograms.	Mean corpuscular hbg., conc., %.	Carbon dioxide combining power.	Diacetic acid and acetone urine.	Blood sugar mg. %	Years of diabetes.	Age.	Sex.
43	4.49	13.3	38.3	85	30	35	9	+++	340	−1 mo.	6	F
24 H	4.50	13.2	40.0	89	29	33	..	+				
96 H	4.45	12.6	39.0	88	28	32	Normal	0				
44	5.01	14.2	42.0	84	28	34	22	++	316	2 yrs.	11	F
48 H	5.37	15.3	45.0	84	28	34	..	0	110			
96 H	5.09	13.9	45.1	89	27	31	..	0				
6 D	5.23	13.9	46.3	89	27	30	Normal	0				
45	6.03	14.5	45.0	75	24	32	14	++	230	−1 yr.	13	F
48 H	5.23	13.9	38.0	73	27	37	..	0				
5 D	4.80	11.9	42.0	88	25	28	..	0				
7 D	5.04	12.8	41.5	83	25	31	40	0				

TABLE 2A.—DIABETIC ACIDOSIS (ADULTS).

Case No.	R.B.C., millions/c.mm.	Hbg., gm./1000 cc.	Volume packed R.B.C., cc./100 cc.	Corpuscular volume, cubic microns.	Corpuscular hbg., micro micrograms.	Mean corpuscular hbg., conc., %.	Carbon dioxide combining power.	Diacetic acid and acetone urine.	Years of diabetes.	Age.	Sex.
46	4.83	..	53.4	111	..	..	11.7	++++	..	32	M
6 H	4.72	..	43.7	93	..	..	13.5	++++			
12 H	4.72	..	41.2	88	..	..	57.9	0			
24 H	3.06	..	29.0	93	..	..	65.5	0			
47	5.02	..	55.0	109	..	..	7.1	++++	4+	47	F
19 D	3.00	..	34.5	115	..	..	?	0			
48	4.38	11.0	48.1	110	26	23	13.0	++++	2	21	F
49	4.90	12.1	48.0	98	25	25	25.8	++++	2½	17	F
50	4.80	..	46.9	98	..	..	29.6	+	..	..	M
5 H	4.65	..	42.6	92	..	..	?	0			
16 H	4.57	..	37.6	82	..	..	57.9	0	..	37	
4 D	4.67	12.4	37.1	80	..	33	Normal	0			
51	5.74	..	55.4	97	..	..	12.6	++++	−1	17	F
24 H	4.75	..	45.0	95	..	..	39.0	0			
52	5.00	..	48.0	96	..	..	27.7	+++	..	26	M
53	5.10	15.0	48.0	94	29	31	15.0	++++	1+	36	M
24 H	4.28	12.1	36.0	84	28	34	41.2	+			
54	5.31	16.0	50.0	94	30	32	28.0	+++	..	46	F
24 H	4.60	15.6	41.0	89	34	38	42.8	0			
55	4.76	13.8	44.5	94	29	31	39.0	++++	1+	25	M
Readmission											
4 M	6.30	19.0	54.5	87	30	35	24.5	++++			
56	5.49	..	50.0	91	..	..	11.7	++++	..	14	F
12 H	4.91	..	38.0	77	..	..	82.4	0			
Readmission											
1 M	5.92	..	49.0	83	..	..	10.7	++++			
7 H	4.65	..	37.0	79	..	..	31.5	+			
Readmission											
18 M	5.64	..	52.0	93	..	..	14.0	++++	..	16	F
24 H	4.18	..	39.0	93	..	..	43.8	0			
Readmission											
4 M	3.90	..	35.3	91	..	..	43.9	0			
Readmission											
2 M	5.56	..	45.2	81	..	..	24.0	+++			
57	6.50	..	59.1	91	..	..	25.8	++++	..	..	M
4 H	5.18	..	42.7	83	..	..	46.6	+			
58	5.50	14.9	48.0	87	27	31	13.5	++++	6	24	F
3 D	4.52	14.2	41.7	92	31	34	51.4	++			
59	7.10	19.6	56.0	79	28	35	14.6	++++	5	21	F
36 H	4.19	13.5	37.0	88	32	36	35.3	++++			
60	5.30	..	46.0	87	..	..	24.0	++++	−1	24	M

56 as a single case, then there would be a total of 20 cases, 35% of these having a corpuscular volume of 95 cu.μ, or over, and 55% a corpuscular volume of 93 cu.μ, or over.

TABLE 3.—DIABETIC DWARFS.

Case No.	R.B.C., millions/c.mm.	Hbg., gm./100 cc.	Volume packed R.B.C., cc./100 cc.	Corpuscular volume, cubic microns.	Corpuscular hbg., micro micrograms.	Mean corpuscular hbg., conc., %.	Blood sugar, mg. %.	Diacetic acid and acetone urine.	Years of diabetes.	Age.	Sex.
61	3.96	13.3	37.8	96	34	35	180	0	7	19	F
7 D	4.34	14.2	39.9	92	33	36					
62	3.94	12.6	36.0	92	32	35	200	0	11	14	M
63	5.52	15.1	49.7	90	27	30	190	0	15	21	F
64	4.66	12.4	39.5	85	27	31	..	0	7	13	M

3. Blood studies on 4 diabetic dwarfs are recorded in Table 3. Each of these patients had very large livers; in 3 instances the liver reached the umbilicus, and, in 1, it was about 1 inch above the umbilicus. In only 1 of these 4 patients was the corpuscular volume found to be above 95 cu.μ. The highest value found in any of the other 3 was 92 cu.μ.

Discussion. The volume of the red blood cell was found to be 95 cu.μ, or above, in 14.3% of 42 uncomplicated diabetics. If, as Wintrobe[16c] found, the mean corpuscular volume in the normal person is only 95 cu.μ, or above, once in 49 instances, then the mean corpuscular volume in uncomplicated diabetes was 95 cu.μ, or above, 7 times more often than in the normal person.

The diameter of the red blood cells was measured, and, from these measurements, the thickness of the cells was computed in 2 instances (Cases 1 and 3, Table 1). The diameter of the red cells was found to be within normal limits in both cases, 7.12 μ and 7.64 μ, respectively. The cell thickness was slightly increased in both instances, 2.56 μ and 2.08 μ, respectively. Although there are only 2 cases, far too few to draw conclusions, the results support the work of Holler and Kudelka[10] and Hamburger.[7] Paxton,[14] however, measured the cell diameter in 2 cases of diabetic acidosis and found the diameter to be slightly increased. It is his opinion that the shape of the cell is not changed in diabetic acidosis.

Presumably, there is some substance present, or some change in the already existing substances in the blood of diabetics, which occasionally influences the shape and corpuscular volume of the red blood cells.

In only 1 instance (Case 29) was diacetic acid or acetone found in the urine of an uncomplicated diabetic at the time the blood study was made. In this instance the corpuscular volume was well

within normal limits. It is, therefore, unreasonable to attribute the changes in the red blood cells of uncomplicatsd diabetics to acidosis. The blood sugar appeared to have no relation to the corpuscular volume. Blood sugars were done on 30 of the 42 uncomplicated diabetics and were found to be low as well as high when the corpuscular volume of the red cell was either below 85 cu.μ, or above 95 cu.μ (Fig. 1).

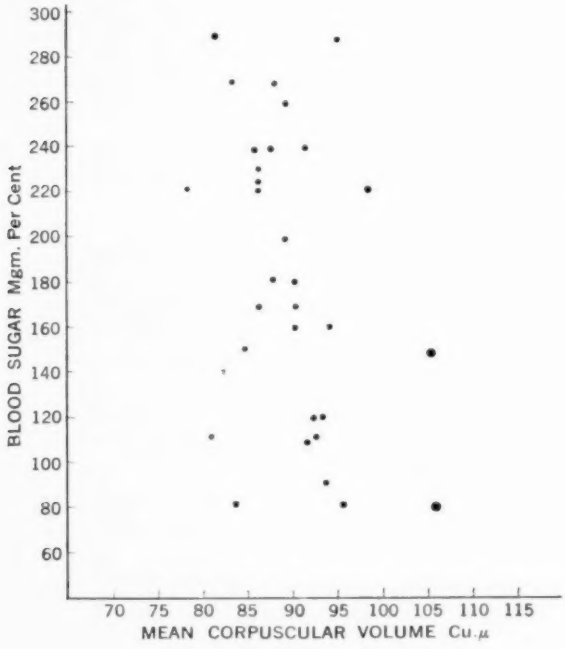

FIG. 1.

Normal values for mean corpuscular volumes in children between the ages of 3 and 13 years, are given by Osgood[12,13] as averaging 73 cu.μ ± 3. Guest[5,6] gives a slightly higher figure, 78 cu.μ to 80 cu.μ. The normal value given by both Guest and Osgood is somewhat lower than Wintrobe's[16a] average normal value for the adult, 82 cu.μ to 92 cu.μ.

Accepting these values for children as normal, then 2 of the children (Cases 43 and 44, Table 2) were found to have corpuscular volumes slightly above normal. The mean corpuscular volume of 1 child (Case 45) was about normal. There was diacetic acid and acetone present in the urine in all 3 cases and the carbon dioxide combining power was quite low. In each, as the acidosis became less, the corpuscular volume actually increased.

Considering the cases readmitted (Cases 55 and 56, Table 2A) as individual cases, 35% of 20 adults with diabetic acidosis were found to have the corpuscular volume above 95 cu.μ.

In this group of adults with diabetic acidosis, there is no relation between the mean corpuscular volume and the degree of acidosis, as evidenced by the carbon dioxide combining power and the

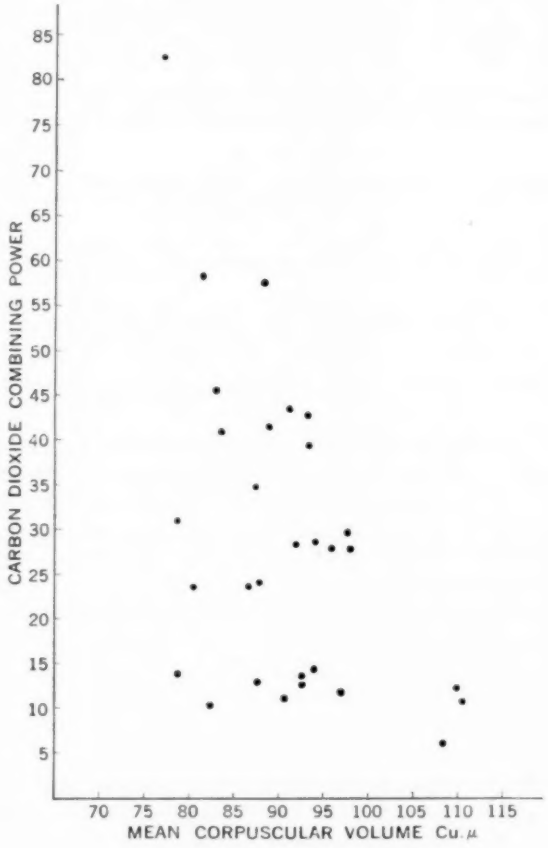

FIG. 2.

presence of diacetic acid and acetone in the urine. Case 55 was admitted to the hospital on 2 occasions. At the time of the first admission, the carbon dioxide combining power was 39 and there was considerable diacetic acid and acetone in the urine. At this time, the mean corpuscular volume was found to be 94 cu.μ. Four months later, the patient was readmitted and, at this time, the carbon dioxide combining power was lower: 24.5. Again there was con-

siderable diacetic acid and acetone in the urine. The corpuscular volume of the red cells at this time was also lower: 87 cu.μ. Because of the patient's lack of coöperation in her own treatment, Case 56 has been readmitted many times. In this case, also, there is no relation between the degree of acidosis and the mean corpuscular volume (Fig. 2).

If, then, the actual degree of acidosis does not affect the volume of the red blood cells in diabetes, what other factor does affect the corpuscular volume? Why should the same individual in acidosis at one time have a slightly elevated corpuscular volume, and, at other times, also in acidosis, have a normal corpuscular volume? It is interesting to note that Elias and Kaunitz[3] demonstrated a change in the average volume of the red blood cells in rabbits which were subjected to a lack of oxygen. They did this by keeping the rabbits in an air pressure which corresponded to an altitude of 5000 to 6000 meters. They found the corpuscular volume to increase from the average normal of 65 cu.μ to 87 cu.μ when the rabbits were subjected to the low oxygen tension. These rabbits, on another occasion, were again subjected to a low oxygen tension, but this time were fed carbohydrates during their exposure to the low tension. The corpuscular volume, when carbohydrates were given, remained normal.

Could it be possible that this is the factor which is of importance in diabetics? Children frequently go into coma suddenly, having probably been on a normal diet up to that time. The adults who are found to have a normal corpuscular volume may have been on moderately high carbohydrate diets and adhered to their diet. Those who are found to have a higher corpuscular volume may have been on high-fat diet or may have decreased their carbohydrates and added more fat to their diet.

In view of the fact that the intake of carbohydrate has considerable effect on the water balance and protein metabolism, is it possible that a combination of these factors, rather than acidosis *per se*, influences the mean volume of the red blood cells?

The 4 cases in Table 3, the diabetic dwarfs, were included in this paper only because these cases had enlarged livers. In only 1 instance was the corpuscular volume found to be above the normal value.

Summary. Studies of the red blood cell counts, hemoglobin and hematocrit determinations have been made in 42 cases of uncomplicated diabetes mellitus, 18 cases of diabetic acidosis, and 4 cases of diabetic dwarfism.

The mean corpuscular volume was found to be 95 cu.μ, or above, in 14.3% of the uncomplicated diabetic and in 35% of the cases of diabetic acidosis. This increase in corpuscular volume of the red blood cells could not be attributed to the acidosis *per se*.

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DIFFERENTIAL DIAGNOSIS OF TRAUMATIC ANEURYSM AND ARTERIOVENOUS FISTULA.

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The physical phenomena associated with arteriovenous fistula are almost pathognomonic for the lesion, yet, "traumatic aneurysms" involving medium sized arteries introduce real problems in differential diagnosis. A history of trauma and a local thrill and bruit are similar and common to both conditions. Significant cardiac enlargement, wide arterial pulse pressure and Branham's[1] phenomenon are cardinal signs observed in an arteriovenous communication; however, at times, because of the small size of the involved vessels or the fistulous opening, these associated alterations in the cardiovascular apparatus are not sufficiently evident to be of diagnostic significance. In a recent study[4] it was shown that there is a definite elevation of venous pressure and a marked increase in the velocity of blood flow in the veins leading from the fistulous connection to the heart. During the progress of this study there were observed patients who had pulsating masses accompanied by continuous bruits and thrills and histories of regional injury similar in nature to the usual accidents leading to arteriovenous fistula, and in whom the differentiation from traumatic aneurysm was seemingly impossible with the use of the established physical phenomena. It became apparent that the use of venous pressure estimations and velocity of blood flow in the vein proximal to the fistulous connection offered a simple, yet definite, method of differentiating traumatic arteriovenous fistula from aneurysm.

Methods. The venous pressure determinations were made by the technique and with the apparatus of Moritz and vonTabora.[3]

The velocity of blood flow was measured with the use of the sodium cyanide method of Robb and Weiss.[5]

The following cases have been selected to illustrate the application and significance of this method of differential diagnosis in traumatic arterial lesions.

CASE 1.—A white male, aged 31, who 6 weeks previously was in an automobile accident, sustained from a piece of windshield glass a stab wound at the cubital fossa of the left arm. Soon thereafter he noticed a pulsating mass in the area over which he felt a "peculiar sensation." He was referred for treatment with the diagnosis of a traumatic arteriovenous fistula.

Physical Examination. In the left cubital fossa there was a pulsating mass, approximately 3 by 2 cm. in size, over which a continuous thrill was noted by palpation and a continuous bruit with a definite systolic accentuation by auscultation. The neighboring veins were moderately dilated. The blood pressure was systolic 130 mm. Hg. and diastolic 75 mm. Hg. When the pulsation and thrill were abolished by pressure, the pulse did not slow, which was a negative Branham's phenomenon, nor was there a significant change in the arterial blood pressure. The teleroentgenogram showed the heart to be 13.4 cm. in transverse diameter with a cardiothoracic ratio of 51%. The venous pressure estimation and velocity of blood flow, using the median basilic vein both on the right and left (involved side), are shown in Fig. 1.

Operation demonstrated a traumatic aneurysm of the brachial artery 1 cm. above its division. There was no arteriovenous communication.

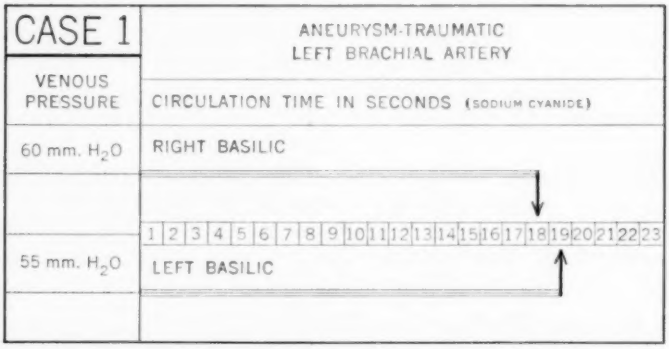
CASE 1
ANEURYSM-TRAUMATIC
LEFT BRACHIAL ARTERY
VENOUS PRESSURE
CIRCULATION TIME IN SECONDS (SODIUM CYANIDE)
60 mm. H_2O
RIGHT BASILIC
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23
55 mm. H_2O
LEFT BASILIC

FIG. 1.—Circulation time in seconds and venous pressure in millimeters of H_2O.

CASE 2.—A negro male, aged 28, was referred with a provisional diagnosis of syphilitic aortitis with aortic regurgitation and a pulsating mass in the right popliteal fossa. The patient stated that he had been having cramps in the leg precipitated by effort for a period of about 6 weeks. He had noticed a swelling in the popliteal area for about 4 weeks, and for 2 weeks the knee had been stiff and painful. The right ankle had been slightly swollen since the development of dysfunction in the right knee. The past history was not significant with the exception of an ice-pick stab wound located in the inner aspect of the right knee, which he stated had penetrated very deeply into the knee.

Physical Examination. Located in the right popliteal fossa there was a pulsating non-tender tumor over which there were a distinct systolic thrill and bruit, but there was a difference of opinion as to whether the bruit was continuous in type with a systolic accentuation. The veins below and around the right knee were moderately dilated. The heart was definitely enlarged to physical examination, and the teleroentgenogram showed the

cardiac shadow to be 15.6 cm. in transverse diameter with a cardiothoracic ratio of 54%. A systolic murmur was heard over the aortic area and a characteristic diastolic murmur of aortic regurgitation in the same area and down the left sternal border. The arterial blood pressure was systolic 140 mm. Hg and diastolic 60 mm. Hg. Branham's phenomenon was negative; however, the changes in the dynamics of the circulation resulting from the free aortic insufficiency invalidated the significance of the results. The venous pressure estimations and velocity of blood flow in the right and left femoral veins are shown in Fig. 2.

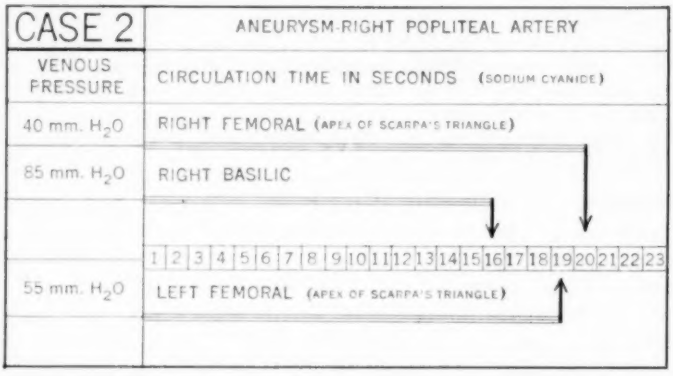
CASE 2
ANEURYSM-RIGHT POPLITEAL ARTERY
VENOUS PRESSURE
CIRCULATION TIME IN SECONDS (SODIUM CYANIDE)
40 mm. H2O
RIGHT FEMORAL (APEX OF SCARPA'S TRIANGLE)
85 mm. H2O
RIGHT BASILIC
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23
55 mm. H2O
LEFT FEMORAL (APEX OF SCARPA'S TRIANGLE)

FIG. 2.—Circulation time in seconds and venous pressure in millimeters of H_2O.

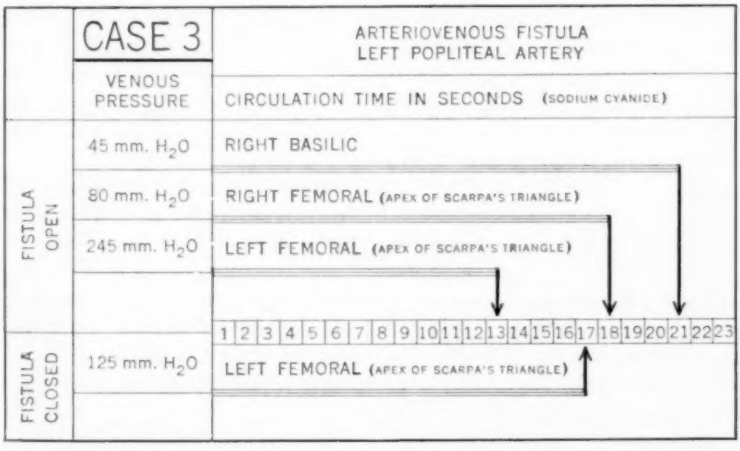
CASE 3
ARTERIOVENOUS FISTULA
LEFT POPLITEAL ARTERY
VENOUS PRESSURE
CIRCULATION TIME IN SECONDS (SODIUM CYANIDE)
FISTULA OPEN
45 mm. H2O
RIGHT BASILIC
80 mm. H2O
RIGHT FEMORAL (APEX OF SCARPA'S TRIANGLE)
245 mm. H2O
LEFT FEMORAL (APEX OF SCARPA'S TRIANGLE)
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23
FISTULA CLOSED
125 mm. H2O
LEFT FEMORAL (APEX OF SCARPA'S TRIANGLE)

FIG. 3.—Circulation time in seconds and venous pressure in millimeters of H_2O.

Operation demonstrated an aneurysm of the right popliteal artery probably syphilitic in nature.

CASE 3.—A negro male, aged 38, was referred for treatment of an ulcer 3 by 5 cm. located on the lower part of the left leg. The patient stated that 14 years before he was shot in the left popliteal space, the bullet penetrating the thigh. The wound healed promptly. Since then he had worked as a

laborer with no subjective symptoms. The left leg had been moderately swollen for many years, but the ulcer had been present for only 9 weeks.

Physical Examination. There was brawny edema of the lower half of the left leg and a healing ulcer on the inner aspect just above the ankle. The veins below and around the knee were moderately enlarged and distended. In the popliteal space a pulsating, non-tender tumor could be seen and felt. Over the tumor there were a continuous thrill and a continuous bruit, having a systolic accentuation and machine-like quality. When the bruit and thrill were eliminated by pressure, the pulse slowed from 80 to 62 per minute, and the blood pressure increased from systolic 132 mm. Hg and diastolic 70 mm. Hg to systolic 144 mm. Hg and diastolic 82 mm. Hg. The heart was definitely enlarged to percussion and the teleroentgenogram showed the transverse diameter to be 16.2 cm. with a cardiothoracic ratio of 56%. The venous pressure estimations and the velocity of blood flow in the right and left femoral veins with the fistula opened and closed by pressure are shown in Fig. 3.

Operation demonstrated an arteriovenous fistula connecting the left popliteal vein and artery.

Comment. The differential diagnosis in Case 1 was impossible with the use of the usual methods employed in the examination of patients with traumatic aneurysm and arteriovenous fistula. Normal venous pressure and velocity of blood flow in each arm were positive data favoring traumatic aneurysm, the diagnosis confirmed at operation.

Case 2 was most confusing. The history of local trauma, dilated regional veins, and the pulsating tumor in the popliteal space were findings common to both aneurysm and arteriovenous fistula. The aortic lesion resulting in changes in heart size, blood pressure and pulse rate similar to those seen in arteriovenous fistula further confused the differential diagnosis. The venous pressure and velocity of blood flow were slightly lower on the side of the lesion. The difference was not significant, and was accounted for by partial compression of the popliteal vein by the aneurysmal sac.

Case 3 illustrates typically the changes in venous pressure and velocity of blood flow occurring in arteriovenous fistula. The failure of compression to completely restore to normal the venous pressure and rate of blood flow is probably due to the collateral circulation around the fistulous connection. Extensive collateral circulation was demonstrated at the time of the operation, and it is felt that this technique of study may be an index to the degree of collateral blood flow and, therefore, a useful guide to the safety of surgical resection of the connecting artery and vein.

Summary. A technique is described for the positive differential diagnosis of traumatic aneurysm and arteriovenous fistula, and 3 illustrative cases are discussed.

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FALSE-POSITIVE WASSERMANN REACTIONS IN INFECTIOUS MONONUCLEOSIS.

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There are several diseases of known etiology, distinct from syphilis, in the course of which serologic tests for syphilis may become temporarily positive. Of this group, the notable members are malaria, yaws, relapsing fever, trypanosomiasis, rat-bite fever, and leprosy. Not infrequently, however, the suspicion of a coexistent latent syphilis is eliminated with difficulty so that the false-positive character of such a Wassermann reaction cannot be indisputably established. Infectious mononucleosis, of unknown causation, typically affects children and young adults in whom the presence of an unrecognized syphilitic infection is reasonably unlikely. It is the purpose of this report to present data concerning 6 cases of infectious mononucleosis in the course of which the complement-fixation, the Eagle flocculation test, or both reactions became temporarily positive. These were discovered among 60 cases of infectious mononucleosis, observed in the past 5 years, in 37 of which one or another of the tests for syphilis was carried out, so that the incidence of transitorily positive serologic reactions was 16%. In all 6 cases to be discussed (Table 1) the diagnosis was established by the clinical course, confirmed by a characteristic blood smear and a positive Paul-Bunnell test.

Table 1.—Wassermann Reaction and Eagle Test in 6 Cases of Infectious Mononucleosis.

Case.	Day of disease.	White blood cell count.	Lympho-cytes, %.	Sheep-cell antibody titer.*	Complement-fixation test.	Eagle test.
1. I. W.	7	10,000	46	..	44	Negative
	10	...	..	1:1024	44	Negative
	16	...	..	..	44444420	Negative
	24	...	..	1:256	Negative	Negative
	37	...	..	1:64	Negative	Negative
2. W. D.	12	17,200	80	1:2048	44	
	14	15,800	..	1:2048	44	Doubtful
	19	6,200	86	1:512	2244442	Negative
	48	6,800	66	..	Doubtful	Negative
	61	7,080	35	1:64	Negative	Negative
3. R. B.	20	8,750	74	1:2048	Negative	Doubtful
4. M. R.	16	12,250	69	1:1024	024444	Negative
	28	...	..	1:2048	Negative	Negative
5. H. B.	10	7,960	75	1:128	44	Positive
	15	11,900	..	1:64	002222	Negative
	17	...	..	..	002222	Negative
	27	7,600	62	1:32	Negative	Negative
6. H. R.	16	16,200	62	..	222000	Positive
	18	11,250	55	1:64	024200	Doubtful
	24	7,040	65	1:32	020000	Negative

* Normal up to 1:16.

Case Reports. Case 1.—I. W., a white female student, aged 16, whose presenting symptoms were fever and epistaxis, showed on physical examination purpura, a palpable liver and spleen. In view of the platelet count of 72,000 and the positive Paul-Bunnell test, it is assumed that this is one of the rare instances of the thrombocytopenic form of infectious mononucleosis. The Eagle test was negative throughout, while the Wassermann reaction was positive from the 7th to the 16th day of the disease. Within the following 8 days it fell to normal from a high titer of 1 to 150.

Case 2.—W. D., a white male student, aged 16, whose chief complaints were stiffness of the neck, sore throat and fever, showed on examination follicular tonsillitis, general glandular enlargement and splenomegaly. The Wassermann reaction was positive from the 12th through the 19th day; on the 48th day after the onset of the illness it was doubtful. On one occasion the Eagle test was doubtful; otherwise, it was negative.

Case 3.—R. B., a white female student nurse, aged 20, who suffered from the anginose variety of the disease, was found to have follicular tonsillitis, general glandular enlargement and an enlarged spleen. A Wassermann test on the 20th day of her illness was negative, the Eagle test was doubtful.

Case 4.—M. R., a white female student, aged 20, was admitted to the hospital on the 15th day of an illness characterized by fever, headache, vomiting and mild sore throat. Examination showed moderate injection of the pharynx, enlarged cervical, and submental glands and a palpable spleen. On the following day, the Wassermann reaction was strongly positive, the Eagle test negative. At the same time, although the patient had never received typhoid inoculations, there were demonstrated in her blood agglutinins for *B. typhosus* (1:640), *B. paratyphosus A* (1:320) and *B* (1:640). These were present in the same concentration 12 days later, when the Wassermann had become negative coincident with a slight increase in titer of the Paul-Bunnell test.

Case 5.—H. B., a white male medical student, aged 24, represented one of the more severe cases with intermittent fever to 104° during the first 10 days of the illness. His only symptoms during that period were chills and sweats, followed later by sore throat. Physical findings of note included an injected pharynx, general glandular enlargement and splenomegaly. On the 10th day both Wassermann and Eagle tests were positive. Within 5 days the latter had become negative; the former considerably reduced. In another 12 days the Wassermann, too, was negative.

Case 6.—H. R., a white male medical student, aged 23, was only mildly ill for 3 weeks with temperature never over 100.4°. The onset was accompanied by pain in the neck, headache and sore throat. Examination on the 16th day showed an injected throat with some exudate, general glandular enlargement and a palpable spleen. Here, again, both Wassermann and Eagle tests were positive over a period of 8 days. It should be noted, moreover, that the Paul-Bunnell test was only moderately positive with a titer of 1:64, in contrast with titers of over 1:1000 in most of the other cases.

Discussion.—In 6 cases of infectious mononucleosis the Wassermann reaction became temporarily positive in 5; the Eagle test positive in 2, doubtful in 2 others. It should be emphasized that the evanescent character of these positive serologic reactions mitigates against the likelihood of recognizing all the instances in which they occur. For example, had Case 5 entered the hospital on the 15th day of the disease rather than on the 10th, a routine Wassermann (not titered) and the Eagle test would have been negative, so that the situation would not have been investigated further. It is

reasonable to assume, therefore, that if these serologic tests were carried out more regularly and persistently, the incidence of positive reactions encountered would be considerably higher than is recorded in the present series. The Paul-Bunnell test may remain positive for 6 months or more. Similarly, the miscellaneous bacterial antibodies that not uncommonly appear in the blood of patients with infectious mononucleosis (Case 4) typically persist for many months while the longest duration of a positive Wassermann was 9 days (Case 1); of the Eagle test even a briefer period.

Scattered references to the occurrence of false-positive Wassermann or allied tests in infectious mononucleosis have appeared. Löhe and Rosenfeld[6] record the case of a 40-year-old woman who probably suffered from the anginose form accompanied by erythema nodosum. Her Wassermann and Meinicke tests were positive from the 14th to the 74th day of the illness. Radford and Rolleston[8] report "2 cases of glandular fever simulating typhus" in a mother and daughter both of whom had positive Wassermann's as late as 6 and 8 weeks after the onset of their respective illnesses. That these reactions may have indicated the coëxistence of syphilis is made likely by the failure of the tests to revert to negative within the period of observation, and by the discovery of syphilis in the father. Parkes Weber and Bode[9] describe 3 cases in whom a temporarily positive Wassermann was observed in all 3, a transitorily positive Meinicke test in 2.

Gooding[4] published an excellent account of an epidemic of infectious mononucleosis which occurred in London in 1930. During the first 3 or 4 weeks of illness, positive or doubtful Wassermann reactions were recorded in 16 of the 27 cases, while a number of these individuals showed positive Kahn tests as well. Hatz[5] reported the case of a patient with infectious mononucleosis whose Wassermann reaction was positive on the 10th, 16th and 21st days of the disease and thereafter became negative spontaneously. The Kline test was negative throughout, while the Paul-Bunnell test was positive to a titer of 1:32 during the period when the complement fixation test was positive.

It is plain, then, that in the course of infectious mononucleosis one may encounter serologic reactions indistinguishable from those characteristic of syphilis. In a previous report,[2] on the basis of our first 2 cases, it was assumed that since the complement-fixation test might become positive, while the flocculation test remained negative, the substance responsible for such a reaction could not be reagin. When later events showed that both tests could be positive, one must conclude that reagin or a closely allied substance, was present in these abnormal sera. That these tests are independent of the presence of the sheep-cell antibodies is evidenced by three facts: first, that partial removal of sheep-cell agglutinins makes the complement-fixation test more positive rather than decreases its strength

(so that any binding effect of these agglutinins upon the sheep red-blood cells to prevent hemolysis is inconsequential);[2] second, that a positive Wassermann occurred in the presence of low titers of sheep-cell antibodies (Cases 5 and 6) while a negative Wassermann was met with in the individual having the highest titer in our series (1:33,000); third, that sheep-cell antibodies may persist for many months after the Wassermann test has become negative and may even increase in titer coincident with a reversion of the Wassermann to negative (Case 4).

In a previous paper[2] it was noted that, not infrequently, miscellaneous bacterial agglutinins are encountered in the sera of patients suffering from infectious mononucleosis. More recent cases have confirmed this observation (Case 4). Subsequently Belk[1] described in detail the presence in the blood of a patient with this disease of an isoagglutinin, an autoagglutinin, 4 distinct heteroagglutinins and a rouleau-forming property, thus reëmphasizing the versatility of antibody responses in infectious mononucleosis.

It is commonly stated that a false-positive Wassermann reaction may occur in thrombocytopenic purpura, although I can find no specific reference in the literature to such a happening. While the thrombocytopenic variety of infectious mononucleosis is uncommon (1 case in the present series of 60) the possibility suggests itself that these rare instances of purpura with false-positive serologic reactions may rather be examples of infectious mononucleosis with reduced platelets. Case 1 was not recognized as infectious mononucleosis until the positive Paul-Bunnell reaction was reported, so that, had this test not been carried out, the final diagnosis would have been purpura hemorrhagica rather than infectious mononucleosis with thrombocytopenia and a false-positive Wassermann reaction. Whenever, therefore, in the course of any disease a Wassermann, suspected of being falsely positive, is encountered, a Paul-Bunnell test should be performed. Should the latter be positive, this is further confirmation of such a suspicion, but a negative test for sheep-cell agglutinins does not necessarily indicate that the patient suffers from syphilis. In a case of rat-bite fever, recently studied, the Wassermann reaction became temporarily positive without any clinical evidence of syphilis, whereas the Paul-Bunnell test was negative.

The problem of why a person suffering from infectious mononucleosis should occasionally develop a false-positive Wassermann is one of great theoretical interest. But since no certain explanation for the Wassermann reaction in syphilis itself is accepted, one can only suggest by analogy that the causative agent of infectious mononucleosis contains a substance having antigenic properties in common with the treponema pallida; or else that this causative agent may liberate from the tissues of the patient a reagin-like material. It is pertinent to recall that among the several organisms that have been suggested as the etiologic factor, at least 3 are protozoal in nature.

Repeated attempts have been made to incriminate Vincent's spirochete, since infectious mononucleosis is so commonly associated with a Vincent's throat infection. Bland[3] claims to have produced in rabbits and monkeys, a disease resembling infectious mononucleosis with a protozoön of the genus Toxoplasma, isolated from the blood of a human case. Third, Mazet,[7] in Nice, demonstrated in blood smears from a patient with infectious mononucleosis a pleomorphic organism, sometimes contained within the red cells, which in one of its forms was morphologically identical with the spirochete of syphilis. While the relationship to infectious mononucleosis of none of these organisms has been proved, the fact that the majority of diseases which may be associated with a false-positive Wassermann are caused by protozoa, would suggest that the causative agent of infectious mononucleosis may likewise be a protozoön.

Summary.—Transitorily positive serologic tests for syphilis were encountered in 6 out of 37 cases of infectious mononucleosis. During the acute stage of the disease the Wassermann test, the Eagle test, or both reactions became positive to high titers but spontaneously reverted rapidly to negative. These positive tests are independent of the presence of sheep-cell antibodies in the patient's serum and indicate, as does the occasional occurrence of miscellaneous bacterial antibodies, the versatility of antibody responses in infectious mononucleosis. In any instance of apparent purpura hemorrhagica with a false-positive Wassermann reaction a Paul-Bunnell test should be performed in order to establish the possible diagnosis of the thrombocytopenic variety of infectious mononucleosis. Reasons are stated for suspecting that the causative agent of infectious mononucleosis may be a protozoön.

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TUBERCULOSIS OF INTESTINES IN TUBERCULOUS ANTHRACOSILICOSIS.

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Anthracosilicosis is frequently complicated by pulmonary tuberculosis. In his study of 418 anthracite coal miners treated at this Sanatorium, Sokoloff[10] states that 237 (56.7%) had pulmonary

tuberculosis. Among 100 cases of anthracosilicosis which came to necropsy at the Sanatorium, Dr. Walsh[11a] found evidence of pulmonary tuberculosis in 86. In view of the high prevalence of pulmonary tuberculosis in anthracosilicosis, a study of the frequency with which intestinal tuberculosis may occur in patients with the combined diseases should be of value.

The present communication reports the incidence of intestinal tuberculosis in tuberculous anthracosilicosis and all statements in regard to anthracosilicosis presuppose the presence of tuberculosis. The incidence and extent of the intestinal involvement and their relationship to the degree of anthracosilicosis, type of pulmonary tuberculosis, and the age of the cases are described. The above findings are compared with those in pulmonary tuberculosis uncomplicated by anthracosilicosis.

Material Studied and Findings. Between May, 1934, and December, 1937, a complete postmortem examination was made on 42 cases of anthracosilicosis associated with pulmonary tuberculosis and on 75 cases of non-anthracosilicotic pulmonary tuberculosis.

Among the 42 cases of anthracosilicosis, 8 (19%) had intestinal tuberculosis. Of the 75 cases of non-anthracosilicotic pulmonary tuberculosis, 38 (51%) had intestinal tuberculosis.

Arranged in two main age groups, 6 cases of anthracosilicosis were below 30 years; the rest were between 30 and 65. Of the 6 cases below 30, 4 (67%) had intestinal tuberculosis; of the 36 above 30, 4 (11%) had intestinal tuberculosis. Among the 75 cases of non-anthracosilicotic pulmonary tuberculosis, 45 were below the age of 30, whereas 30 were between 30 and 70. Of the younger group, 24 (53%) had intestinal tuberculosis, while among the older group 14 (47%) had intestinal tuberculosis.

Arranged according to the extent of anthracosilicosis, 14 cases had early or moderately advanced and 28 cases had far advanced anthracosilicosis. Of the early or moderately advanced group, 6 cases (43%) had intestinal tuberculosis, whereas in the far advanced group only 2 (7%) had involvement of the intestines.

Grouped according to the type of pulmonary tuberculosis complicating anthracosilicosis, 9 cases (64%) of the 14 early or moderately advanced group had acute caseous lesions, whereas 5 (36%) had fibrotic lesions. Of those having caseous pulmonary lesions, 4 (44%) showed intestinal tuberculosis, while of those having fibrotic lesions 2 (40%) had intestinal involvement.

Among 28 cases of far advanced anthracosilicosis 3 (11%) had acute caseous pulmonary tuberculosis, while 25 (89%) had fibrotic tuberculosis. One case (33%) of the caseous group and 1 (4%) of the fibrotic group showed intestinal lesions. In only 1 of the above 28 cases was the pulmonary tuberculosis minimal; in the rest it was far advanced with cavitation.

Discussion. The prevalence of intestinal tuberculosis in ordinary pulmonary tuberculosis is a well known fact. McCrae[7] states that among 1000 Munich autopsies, 566 (56%) showed intestinal tuberculosis. Rubin[9] found that among his 500 necropsies, 324 (65%) had intestinal tuberculosis. Walsh[11b] observed that 76 cases (76%) of his 100 autopsies at the Phipps Institute had involvement of the intestines. Even higher percentages, 80 to 90%, have been reported.[3] In the light of the above observations, the relative infrequency of intestinal tuberculosis (19%) in tuberculous anthracosilicosis is striking (Table 1).

TABLE 1.—FREQUENCY OF INTESTINAL TUBERCULOSIS.

Pulmonary Tuberculosis.

	Anthracosilicosis present.		Anthracosilicosis absent.		Combined total.	
	No.	%.	No.	%.	No.	%.
Intestinal tuberculosis present	8	19	38	51	46	39
Intestinal tuberculosis absent	34	81	37	49	71	61
Total	42	100	75	100	117	100

TABLE 2.—FREQUENCY OF INTESTINAL TUBERCULOSIS—ACCORDING TO AGE PERIOD.

Pulmonary Tuberculosis.

	Age below 30 years.				Age above 30 years.				Age below 30 years.		Age above 30 years.	
	Anthracosilicosis present.		Anthracosilicosis absent.		Anthracosilicosis present.		Anthracosilicosis absent.		Combined total.		Combined total.	
	No.	%.	No.	%.	No.	%.	No.	%.	No.	%.	No.	%.
Intestinal tuberculosis present	4	67	24	53	4	11	14	47	28	55	18	27
Intestinal tuberculosis absent	2	33	21	47	32	89	16	53	23	45	48	73
Total	6	100	45	100	36	100	30	100	51	100	66	100

It has been recognized that intestinal tuberculosis in pulmonary tuberculosis is more common in the young than in the aged. This is also true in anthracosilicosis associated with pulmonary tuberculosis. Among the miners above the age of 30, only 11% had intestinal tuberculosis, whereas of the younger group 67% showed it (Table 2). The reason appears to be that among the younger miners the degree of anthracosilicosis was less and the pulmonary tuberculosis was more acute. However, age *per se* does not seem to be the determining factor in the incidence of intestinal tuberculosis in the miners.

Table 3 clearly indicates that in early or moderately advanced anthracosilicosis intestinal tuberculosis occurs with practically the same frequency as in non-anthracosilicotic pulmonary tuberculosis. In these cases, pulmonary tuberculosis showed a definite tendency toward rapid spread and destruction. The amount of the intestinal involvement when it occurred was great; often the entire length of the ileum, cecum and other parts of the large bowel were involved. In far advanced anthracosilicosis when intestinal tuberculosis occurred, the lesions, as a rule, were few in number and less extensive.

TABLE 3.—FREQUENCY OF INTESTINAL TUBERCULOSIS ACCORDING TO DEGREE OF ANTHRACOSILICOSIS.

Pulmonary Tuberculosis.

Intestinal tuberculosis.	Anthracosilicosis absent.		Anthracosilicosis present.			
			Early or mod. advanced.		Far advanced.	
	No.	%.	No.	%.	No.	%.
Present	38	51	6	43	2	7
Absent	37	49	8	57	26	93
Total	75	100	14	100	28	100

There is no doubt that intestinal tuberculosis is rare in far advanced anthracosilicosis associated with pulmonary tuberculosis. This, however, does not mean that anthracosilicosis has generally an inhibitory effect upon the development of tuberculosis. On the contrary, Sokoloff[10] found that the incidence of pulmonary tuberculosis increased in direct proportion to the amount of anthracosilicosis. He found that in the first stage of anthracosilicosis 5.4%, in the second stage 24%, and in the third stage 70.1% had pulmonary tuberculosis. However, as far as intestinal tuberculosis is concerned, it became rarer as the degree of anthracosilicosis increased.

The rarity of intestinal tuberculosis in the late stage of anthracosilicosis is very probably due to the presence of pulmonary fibrosis and the customary chronicity of the pulmonary tuberculosis in these patients, as observed by Landis.[5] The cavity when it forms in the center of an anthracosilicotic mass enlarges very slowly. Often such a cavity contains mucoid material having only a few tubercle bacilli or none at all. The cavity wall and the surrounding tissue wall when examined microscopically show very few tubercle bacilli or none at all. Furthermore, the blood-vessels in the anthracosilicotic mass and particularly in the neighborhood of the cavity always undergo extreme sclerosis frequently followed by thrombosis. Blood-vessels completely obliterated by fibrosis are frequently observed.[2,8] Such vascular changes would tend to prevent the spread of tubercle bacilli.

The pathogenesis of secondary tuberculosis of the intestines in the adult is not clearly understood. It may be due to direct infection

by swallowed sputum which contains tubercle bacilli (Karsner[4] and MacCallum[6]) or to a spread through the lymphatics (Aschoff[1]), or to a hematogenous spread. In our study, all cases of intestinal tuberculosis in either the anthracosilicosis or pulmonary tuberculosis group had repeatedly positive sputum of high Gaffky counts; on the other hand, many cases with such sputum had no intestinal lesions. Three of the 8 cases of anthracosilicosis with intestinal involvement had tubercles in the kidneys as well; in these cases the mode of infection may have been through the circulatory system.

In reference to the symptomatology of intestinal tuberculosis, it was interesting to note that in 5 cases of anthracosilicosis having tuberculosis of the intestines there was no complaint whatever suggesting any intestinal lesion. In 3 cases abdominal pain, tenderness in the right lower quadrant, diarrhea, nausea and vomiting were present singly or together from time to time. Walsh[11b] has observed that pain, tenderness, diarrhea and abdominal rigidity, which were considered as the classical symptoms of intestinal tuberculosis, possess no definite diagnostic value. His observation held true in the present study.

The common abdominal complaints among the far advanced anthracosilicotic patients with or without pulmonary tuberculosis are anorexia, vague abdominal discomfort, flatulence and diarrhea alternating with constipation. These symptoms may be due to chronic passive congestion of the gastro-intestinal tract secondary to myocardial weakness, which is a common occurrence in anthracosilicosis.

In view of the preponderance of intestinal tuberculosis in early or moderately advanced anthracosilicosis complicated by acute caseous pulmonary tuberculosis, any persistent abdominal complaints together with rapid loss of weight, high and irregular fever may justifiably lead to the suspicion of tuberculous involvement of the intestinal tract.

Summary and Conclusions. 1. Tuberculosis of intestines is infrequent in tuberculous anthracosilicosis.

2. The postmortem examination of 42 cases of tuberculous anthracosilicosis revealed 8 cases (19%) of intestinal tuberculosis. Among 75 cases of non-anthracosilicotic pulmonary tuberculosis, 38 (51%) showed intestinal tuberculosis.

3. Tuberculosis of intestines when it occurs in the presence of anthracosilicosis is most frequently found in early or moderately advanced anthracosilicosis. In this stage the incidence of intestinal involvement is practically the same as in non-anthracosilicotic pulmonary tuberculosis.

4. In the presence of far advanced anthracosilicosis intestinal tuberculosis is uncommon; only 7% of 28 cases showed intestinal tuberculosis. This relative infrequency of intestinal tuberculosis appears to be due to the extensive fibrosis of the lungs, and the

chronicity of the pulmonary tuberculosis usually present in these patients. A combination of these two conditions apparently tends to prevent the spread of tuberculous infection to other parts of the body.

5. The incidence of intestinal tuberculosis was greater among those under the age of 30 in both anthracosilicotic and non-anthracosilicotic groups. But the age *per se* does not appear to be the determining factor; of the anthracosilicotic cases above the age of 30, 11% had intestinal tuberculosis, while of the non-anthracosilicotic group of the same age period 47% showed intestinal lesions.

6. In the majority of cases of intestinal tuberculosis in anthracosilicosis, there were no symptoms referable to the gastro-intestinal tract. Pain, tenderness, and diarrhea which were present in a few cases could not be depended upon for the diagnosis. The vague abdominal discomfort frequently complained of by anthracosilicotic patients may well be due to chronic passive congestion of the gastro-intestinal tract secondary to gradual myocardial failure.

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THE EFFECT OF SODIUM CHLORIDE DEFICIENCY ON GASTRIC ACIDITY.*

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Little is known about the effect of sodium chloride deficiency on gastric secretion. In clinical studies, it has been impossible to select conditions in which the chloride deficiency is uncomplicated. In the

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following study, an endeavor was made to maintain the subjects in as normal a physiologic state as possible except for limited intake and increased output of chlorides.

The earliest work on the effects of salt deficiency on gastric secretion was done by Rosemann[7a] in 1911. He placed one dog on a salt-free diet, and found that the free hydrochloric acid in the gastric juice diminished gradually to zero. It is questionable whether his data justify his conclusions. Takata[8] (quoted by Rosemann) could not confirm these results experimentally. Rosemann[7b] in a later paper attempted unsuccessfully, it appears to the writer, to reconcile his conclusions with those of Takata. Fruin,[4] using dogs with a Pavlov pouch, found that a low salt diet caused diminution of gastric juice and a decrease in hydrochloric acid, although the total chlorides remained the same. In later experiments, Dragstedt and Ellis[2] showed that in dogs rendered hypochloremic the amount of free and total hydrochloric acid as well as the total chlorides in the gastric secretions remained normal almost to the point of death of the animals.

Eimer[3] found that when normal people were placed on a low salt diet, the gastric hydrochloric acid remained normal or increased. A tendency to a rise in free and total hydrochloric acid was noted by Unverricht[11] in similar experiments. None of the workers who have studied heat-cramps has reported on the hydrochloric acid secretion of the stomach in this condition. Talbott[9] examined the vomitus of 1 patient and found a chloride concentration of 135 mg. per 100 cc. Blood taken shortly before the patient vomited had a serum chloride concentration of 339 mg. per 100 cc. McCance[6] has recently reported the effect of uncomplicated sodium chloride deficiency in man but he did not examine the gastric secretion of his subjects.

Method. The method used in our experiments to produce sodium chloride deficiency followed closely that which was introduced by McCance.[6] Three normal, healthy, adult male volunteers were the experimental subjects: M. H. S., age 29; J. B. L., age 30; and J. C. L., age 27. All 3 continued to perform their usual duties throughout the experiment. Gastric analyses were made each morning at 8 o'clock, the subjects having fasted since 9 o'clock the evening before. Smoking was stopped at midnight and was not resumed until after the test each morning. When a stomach-tube had been passed and a fasting sample withdrawn, 50 cc. of a 7% aqueous solution of ethyl alcohol were ingested through the tube. Samples of the gastric contents were taken 20, 40 and 60 minutes after ingestion of the test meal. Following this, 0.1 mg. of histamine hydrochloride per 10 kg. of body weight was injected subcutaneously into the deltoid region and samples of gastric juice were withdrawn 15 and 30 minutes after the injection. The gastric juice was titrated, using Töpfer's reagent and phenolphthalein as indicators.

Specimens of fasting venous blood were taken each morning immediately prior to the gastric analysis. The whole blood chlorides and plasma chlorides were determined by the method of Whitehorn.[12] Determinations of urea nitrogen and non-protein nitrogen of fasting venous blood were made on the last day of the experiment and again several weeks later.

Urine was collected in 24-hour specimens, terminating at 7 o'clock each morning. A few cubic centimeters of chloroform were added as a preservative. The urinary chlorides were determined by the method of Hawk and Bergeim.[5]

A preliminary control period was established in order to determine the results of the laboratory procedures under normal conditions for each individual. Two of the 3 subjects had tests on 3 mornings, and the third on 1 morning. The experimental period began on the day following the control period, lasted 7 days, and had two objectives: 1, to decrease the sodium chloride intake; and 2, to increase the sodium chloride output.

A dietary régime was outlined by a member of the dietetic staff of the hospital. The caloric intake daily was 1800 to 1900 calories, with at least 45 gm. of protein and from 0.7 to 0.9 gm. of sodium chloride. Most of the salt was contained in bread and butter and as these foods were not always eaten, the figures given above represent a maximum intake. Fluids were taken freely, usually in the form of distilled water. A typical diet is shown in Table 1.

TABLE 1.—A TYPICAL DIET USED DURING THE EXPERIMENT.

	Grams.	
Total intake:	0.754	Sodium chloride
	52	Protein
	117	Fat
	243	Carbohydrate
	2233	Calories
BREAKFAST:	200	Orange juice
		One egg
	60	Salt-free bread
	15	Salt-free butter
	15	Jelly
	30	Pastry cream
		Coffee
LUNCHEON	100	Rice or macaroni
	200	Vegetables from among the following: cabbage, carrots, celery, artichokes, cucumber, string beans, eggplant, squash, tomatoes, corn, peas
	15	Salt-free mayonnaise
	30	Pastry cream
	30	Salt-free bread
	15	Salt-free butter
	15	Almonds
	30	Fresh dates
	100	Fresh fruit from among the following: apples, apricots, peaches, pears, grapes, figs, strawberries
		Coffee
DINNER:	100	Beef, lamb, veal or chicken
	100	Potato
	200	Vegetable as at luncheon
	30	Salt-free bread
	15	Salt-free butter
	15	Salt-free mayonnaise
	30	Pastry cream
	15	Walnuts
	30	Raisins
	100	Fruit as at luncheon
		Coffee

During the experiment, several measures were used to increase sweating. The subjects ate, slept and spent as much time as possible in an air-condi-

tioned room, the temperature of which was maintained constantly at 88° F. and the relative humidity at 35%. This atmosphere was not intolerable but resulted in peripheral vascular dilatation. Sweating was moderate and occasionally profuse, especially at night. All 3 subjects spent half an hour during each of the first 4 afternoons of the experimental period in a radiant-heat bath. This apparatus is standard physiotherapy equipment and consists of a metal box open at one end and heated by several rows of 250-watt bulbs. The subject lies on a covered rubber mattress and the open end of the box is then closed with a blanket leaving his head exposed. The temperature inside rises to 120 to 150° F. within a few minutes, profuse sweating results and continues for a varying period of time up to 2 hours in spite of cold needle-showers. There is an average loss of approximately 1½ pounds during this procedure.

TABLE 2.—GASTRIC ANALYSES.

	8/29/36.		8/31/36.		9/1/36.		9/2/36.		9/3/36.		9/4/36.		9/5/36.		9/7/36.	
	Free.	Total.	Free.	Total.	Free.	Total.	Free.	Total.	Free.	Total.	Free.	Total.	Free.	Total.	Free.	Total.
M.H.S.:																
Fasting	0	6	10	18	24	38	16	32	12	34	12	34	16	20	24	46
20 min.	0	8	26	38	24	34	30	36	24	34	32	38	52	62	44	59
40 min.	0	8	44	56	44	56	42	54	40	58	54	64	74	86	56	72
60 min.	0	10	0	14	44	60	62	78	60	72	56	68	56	70	30	46
Histamine:																
15 min.	0	16	86	98	90	100	78	90	86	94	100	112	96	108	82	96
30 min.	0	12	112	124	106	118	102	110	116	126	114	122	50	60	106	116
J.B.L.:																
Fasting	0	8	16	28	24	34	14	32	0	22	0	14	0	20	0	10
20 min.	48	60	28	38	58	68	32	44	0	14	18	26	34	34	28	38
40 min.	32	46	38	44	68	80	32	42	0	12	24	32	42	54	0	16
60 min.	34	48	26	38	28	38	20	36	10	32	24	36	34	48	26	38
Histamine:																
15 min.	72	84	42	50	82	92	42	52	46	60	46	60	70	82	66	80
30 min.	36	56	68	76	80	90	70	92	64	80	86	94	98	104	92	100
J.C.L.:																
Fasting	..	..	..	..	20	26	0	14	0	14	0	12	0	20	4	12
20 min.	..	..	..	..	16	62	0	8	8	16	10	20	38	44	18	26
40 min.	..	..	..	..	24	38	6	16	10	22	8	16	40	50	20	32
60 min.	..	..	..	..	0	14	0	12	12	28	14	24	14	28	20	34
Histamine:																
15 min.	..	..	..	..	32	46	14	26	36	48	50	62	44	56	66	80
30 min.	..	..	..	..	42	58	30	38	90	100	90	100	94	100	94	104

Results. There was no consistent or significant change in the amount of free or total hydrochloric acid secreted by the stomach during the entire experiment (Table 2). Our findings agree with those obtained by Dragstedt and Ellis[2] in dogs, although the salt deficiency in their animals was more severe. It is difficult to explain the absence of free hydrochloric acid in the subject, M. H. S., on the first day. Gastric analysis 6 years before had been normal. He had a severe histamine reaction but the anacidity had been noted in the specimens withdrawn before histamine was given.

The gradual decrease of the whole blood chlorides in all 3 subjects is shown in Table 3. While the experimental error of these determinations is 3%, there was found to be a fairly uniform tendency for the whole blood chlorides to decrease on each succeeding day. The daily fluctuations of the plasma chlorides are shown in

Table 4. It is well established that the plasma chlorides are maintained at nearly normal levels until the terminal stages of sodium chloride deficiency are reached. The levels of the urea nitrogen and non-protein nitrogen are given in Table 5.

TABLE 3.—WHOLE BLOOD CHLORIDES.

Date, 1936.	Mg. per 100 cc. as chlorine.			Mg. per 100 cc. as NaCl.		
	M.H.S.	J.B.L.	J.C.L.	M.H.S.	J.B.L.	J.C.L.
8/29	287	279	...	473	460	
8/31	295	276	...	486	455	
9/1	285	276	289	470	455	477
9/2	283	273	255	467	450	421
9/3	281	273	261	463	450	431
9/4	256	270	247	422	447	407
9/5	251	264	246	414	435	406
9/7	271	265	252	430.7	437	414

TABLE 4.—PLASMA CHLORIDES.

Date, 1936.	Mg. per 100 cc. as chlorine.			Mg. per 100 cc. as NaCl.		
	M.H.S.	J.B.L.	J.C.L.	M.H.S.	J.B.L.	J.C.L.
8/29	344	356	...	567	594	
8/31	361	355	...	595	589	
9/1	342	344	325	564	570	536
9/2	328	336	340	541	554	551
9/3	305	354	345	503	584	569
9/4	303	341	348	500	562	575
9/5	326	Broken	339	538	Broken	559
9/7	341	348	336	562	574	554

TABLE 5.—NON-PROTEIN NITROGEN AND UREA NITROGEN.

Date. 1936.		(In milligrams %.)		
		M.H.S.	J.B.L.	J.C.L.
9/7	Non-protein nitrogen	48.3	36.6	38.7
	Urea nitrogen	37.5	15.8	18.9
10/20	Non-protein nitrogen	41.9	33.6	
	Urea nitrogen	16.9	14.3	
10/29	Non-protein nitrogen	33.6		
1937.				
4/16	Non-protein nitrogen	....	....	30.0
	Urea nitrogen	....	....	15.5

TABLE 6.—URINARY CHLORIDES AND URINARY VOLUMES.

Date, 1936.	Urinary chlorides (in milligrams as chlorides).			Urinary volumes (in cubic centimeters).		
	M.H.S.	J.B.L.	J.C.L.	M.H.S.	J.B.L.	J.C.L.
8/30	6,062.5	5,883	..	970	2,220	
8/31	7,047	5,772	..	870	2,220	
9/1	10,400	4,346	..	1,225	2,430	
9/2	4,320	3,350	4,220	800	2,795	1,190
9/3	1,010	1,180	1,250	720	2,960	1,780
9/4	384	264	306	590	1,760	3,060
9/5	19	13	25	640	2,590	2,000
9/7	4	6	11	550	2,460	1,520

There was a steady decrease in the urinary excretion of chlorides beginning on the first day. On the last day a few milligrams only were found in the urine (Table 6). These findings confirm

McCance's[6] work. The rise of chloride excretion in one subject, M. H. S., on the last day of his control period was due to increased salt intake on the preceding day following the playing of 3 sets of tennis.

None of the subjects had any notable symptoms until the fourth day of the experimental period. At that time, all 3 had occasional vague muscular cramps and a sense of fatigue. Temporary weakness was felt following the radiant-heat baths. One of the subjects had an indefinite sensation of epigastric discomfort; 2 had eructations and flatus. None of the subjects had pronounced loss of the sense of taste except for vegetables and salt-free bread during the last 2 days, possibly because the salt deficiency was not carried to to the extreme degree of McCance's[6] experiments or because of the attractiveness of the food served. Thirst was noted by all and was not relieved by distilled water. The subject who had the highest urea nitrogen and non-protein nitrogen determinations noticed a dry mouth despite a high fluid intake; also a peculiar taste which was probably due to the excretion of urea in the saliva. All subjects lost weight in amounts varying from 4 to 10 pounds which was regained within 24 hours after the beginning of the recovery period. There was increasing lassitude and desire to sleep during the day. The inability to sleep well at night was probably due to the temperature of the control room. Approximately 30 gm. of salt and large amounts of water were ingested in the first 2 days following the experiment. All 3 subjects developed a marked edema, similar to that seen in acute nephritis. One subject increased in weight by 14 pounds in 24 hours.

Comment. The fact that no significant change occurred in the secretion of hydrochloric acid by the stomach in spite of marked sodium chloride deficiency has a simple explanation. It must be remembered that in the absence of diarrhea, the bowel excretes but a small amount of chloride. This means that most of the chlorides secreted by the stomach must be resorbed lower in the gastrointestinal tract. Thus there would be no advantage to the body economy to suppress secretion of hydrochloric acid in the stomach. The chlorides excreted through the bowel comprise but a small fraction of the chlorides ingested in even a very low salt diet. McCance[6] reported a loss of less than 100 mg. of chloride daily in the feces.

Under normal conditions, the kidneys and sweat glands excrete most of the excess sodium chloride from the body, while only a small amount is excreted through the bowel. McCance[6] showed that when the sodium chloride intake is restricted, the kidneys soon cease to excrete chloride in the urine, that excretion through the bowel is decreased, but that the skin continues to excrete a large amount of sodium chloride until the deficiency becomes extreme.

Consequently, in human subjects measures which increase sweating and decrease intake of sodium chloride are the only ones available to induce salt deficiency in the body. In animals, it is possible to drain the stomach continually by the method of Dragstedt and Ellis,[2] but this is not practicable in human subjects, and furthermore is not a physiologic means of salt excretion.

The appearance of edema during the period of recovery is not an evidence of a severe degree of sodium chloride deficiency. Baird and Haldane[1] and Torbert and Cheney[10] have reported this effect following the ingestion of large amounts of salt by normal people. As might be expected, the edema in the subjects of our experiment was much more marked than that described by these authors. The explanation of this phenomenon is the deposition of water with the excess sodium chloride in the intercellular spaces. Probably the same mechanism causes the edema which appears in chronic nephritics when sodium chloride is added to a previous low salt diet.

The purpose of our work was to determine whether or not loss of chlorides through the sweat causes a decrease in gastric acidity. Since in normal subjects no significant decrease in gastric acidity was found, it is unlikely that loss of chlorides causes the anacidity found in some patients with exophthalmic goiter or with anxiety states complicated by the hyperventilation syndrome.

Summary. Three normal human males were subjected to a state of sodium chloride deficiency by decreasing the sodium chloride in the diet and increasing the excretion of sodium chloride by sweating. The fall in urinary and whole blood chlorides, the rise in urea nitrogen and non-protein nitrogen in 1 of the subjects, and the symptoms which appeared, indicated that a state of sodium chloride deficiency had been established. Deficiency of sodium chloride produced no significant changes in the gastric secretion of either free or total hydrochloric acid in the 3 human subjects studied.

Grateful acknowledgment is due to Josephine Dickison, A.B., A.M., and Florence Selvin, A.B., for the blood and urine chloride determinations made for this study; to Miss Ramona Greefkens for the gastric analyses; to Rosalie C. Silverberg, A.B., for the chloride analyses of the bread and butter, to Eunice Barg, A.B., for the preparation of the diets, and to the physiotherapists for supervising the radiant-heat baths.

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THE ORIGIN OF EMOTIONAL FACTORS IN NORMAL PREGNANT WOMEN.

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(From the Preston Retreat.)

The present study is based on Strecker's[1] recent paper which presents a new thought in obstetric care. The maternity hospital utilized was the Preston Retreat, presenting an ideal service for this particular kind of study, because of the careful economic and social investigation of each family in their home, and direct supervision of each patient by the chief of service in the outpatient clinic as well as in the wards. The material was only 100 cases, of which 50 were adequately followed up, but a report of this small number is justified on the basis of sufficiently definite conclusions. The largest percentage of our patients were of Irish descent, constituting 60 of the group; there were 25 Italians, 10 of German descent, 2 Jewish, and the remaining 3 were of mixed origin. We have no colored patients in the Preston Retreat.

By "normal pregnant women" we mean registered prenatal patients without obvious disease, or the average mother from the point of view of any maternity department in any hospital, since the job is of necessity one of obstetrics. The routine of prenatal, natal, and postnatal care had doubtlessly been carried on with efficiency, yet we are forced to conclude from our study that a few of the so-called normal patients must have been potentially psychotic, and that a majority of them had specialized anxieties relating to pregnancy. It is likely therefore that in any hospital where the service is too large for the chief to have any routine contact with the patient, the possibility of emotional problems, so serious that they might result in puerperal psychoses, might be overlooked, underestimated, or disregarded.

It was the examiner's idea to create a rapport necessary to gain the confidence of the patient for the simple matter of getting facts rather than to establish any sort of transference necessary in dealing with neurotic patients. Sufficient time was given to allow the patients to speak without feeling hurried. An attempt was made to individualize each patient and conduct the interview in relation to the type of person presented. In the event that there seemed more to say than the information we were trying to secure, the patient was seen again and added data secured with as little direction as possible. Sympathy and interest was the rule since we had no idea

of including any psychiatric procedure in our clinic, intending to refer all cases calling for psychiatric therapy.

Our material was taken from a non-selected group and we feel that it represents a satisfactory cross-section of the whole. Of the 100 patients, 50 were adequately followed up after the birth of the infant to determine what measure of adjustment was made and to be used as a comparison between the pregnant woman and the non-pregnant. By an overwhelming majority our patients frankly confessed more anxiety during the period of pregnancy than previously, which was to be expected inasmuch as these women, belonging to a low level in the economic group, reflected anxieties largely related to poverty. From this it may be deduced that most women are more anxious during the period of pregnancy and that the type of anxiety is chiefly conditioned by the economic and social group from which they are drawn.

We present the physical factors associated with this group with the idea that associated complications, though mild, might play a part in influencing states of anxiety. There were in all, syphilis, 2 cases; malnutrition (slight), 10; moderate anemia, 2; pernicious-like anemia (due to pregnancy), 1; mild toxemia of pregnancy, 3; functional heart trouble, 3; organic heart disease, 1; vaginitis, 1; carious teeth, 20; and oral sepsis, 1. Except possibly for the 2 instances of lues, we feel that the physical factors were irrelevant to anxiety states of this group.

Since economic factors seemed to play such an important part in conditioning the axiety of these patients, a short summary of the social-economic picture should be presented. Of these 100 women, 40 had never been pregnant before, 32 were pregnant for the second time, and 28 a third time or over. It was interesting to notice that we had no cases of nausea of the type that might be attributed to psychic rejection of the child. Of the 40 women pregnant for the first time, only 2 rejected the idea of having their infants, the reasons stated were: (1), economic reasons, 1; (2), separated family, 1. In the second group of 3 women each having had 1 child, 3 rejected the idea of having another baby; the reasons for not wanting: (1), economic stress, 2; (2), father serving jail sentence, 1. In the third group of 28 women 12 rejected the idea of having another baby; the reasons for not wanting: (1), economic factors, 10; (2), separation from husband, 1; (3), chronic illness of husband, 1.

It is remarkable that only 17 out of 100 women in adverse circumstances resented their conceptions, since all were aware that economic insecurity was definitely exaggerated by pregnancy. Of the 100 cases, 20 were on relief, 30 had government jobs, and 50 varied temporary work. The average allowance for a family of 3 on relief was $10.20 a week, with an added dollar for each extra child. The average allowance for those who had government positions was $15.00 a week regardless of the size of the family. Various other

miscellaneous jobs averaged $18.00 a week, regardless of size of family.

We have divided our cases into four groups: *a*, good; *b*, temporarily adequate; *c*, fair; *d*, poor; interpreted as follows: by "good" we refer to the type of family where both economic considerations and types of parents promise a satisfactory way of living and an intelligent adjustment to the whole situation. This group, which should improve their general status when the abnormal economic slump has passed, numbered 25. By "temporarily adequate" we indicated families who were under great economic strain but managing well nevertheless, numbering 17. By "fair" we mean families whose funds were inadequate and whose prospects of improved conditions extremely doubtful, of whom there were 25. By "poor" we refer to the families who because of stupidity, ill health and general maladjustment suggest that any improvement would be absolutely impossible, amounting to 33.

Among the 75 women who freely admitted more anxiety during the period of pregnancy, an increase in the degree of anxiety was noted in those women who had 2 or more children. But it appeared that the economic-social situation did not quite account for the whole of this exaggerated anxiety, and in future studies we would like to consider the possibility of some physiologic reason for those women having 2 or more children to be markedly more nervous. Of the total 100, only 3 stated that they were less anxious during pregnancy and 22 said that they felt "about the same."

The specialized types of anxieties were divided into four groups: 1, anxiety relating to economic security, 75%; 2, phobias, 16%; of these 12 expressed fear of death, 2 were concerned with "old wives tales," relating to the child being marked, and 2 had serious phobias concerning their own health; 3, anxieties relating to husband, 7%, of whom 2 were worried about their looks being spoiled, 2 were suffering from the knowledge of infidelity, 2 were deserted by their husbands, and 1 whose husband was serving a prison term; 4, anxiety relating to other members of the family, 10%; of these all were living with their in-laws and felt that there was too much interference. In our total group, there were 3 women who showed marked depression but their situation seemed to justify the state of mind, so were not included in the potential psychotic group noted below. There were only 3 patients who gave histories of previous nervous breakdowns.

Finally, we come to the potentially psychotic mothers. Three of our patients furnish us with an excellent example of why emotional factors in pregnant women should be considered with a full sense of responsibility. We feel these cases important enough to consider somewhat in detail.

Case Reports. CASE 1.—Mrs. H., aged 24, unfortunately did not come under our prenatal observation as a case for special attention since our

neurologic interests had not been aroused at the apparent time of her emotional upset. The word "apparent" is an important item in realizing that a superficial interest in the social and economic set-up, and ordinary routine obstetrical examination is *not sufficient* to detect the subtle processes of possible mental disorder. Therefore our initial knowledge of Mrs. H.'s emotional difficulties occurred when her infant was 6 months old. Although she seemed a well poised, quiet woman, subsequent history taking disclosed the fact that she had "attacks" off and on for many years, culminating in a maniacal state in which she tried to stab her husband with a carving knife. This is her first child, and her background is one of having been sent by her father to live with a foster mother at her mother's death. Mr. H. is out of work, receives $10.20 weekly relief money, is fond of his wife, but is a thoroughly inadequate personality who compensates by bragging. Mrs. H. claims to love her husband, but all of her violent attacks are directed against him. The present period of the wife's mania dates from the time that the husband lost his job and stayed home all of the time. In the absence of physical pathology, we sent this woman to a psychiatric clinic for diagnosis and treatment, delayed by poor patient coöperation.

Case 2.—Mrs. M., white, aged 23. Second pregnancy, one living child, a girl of 3. During the seventh month of her pregnancy she confessed that if she had a male child she seriously did not know what she would do about it, stating that she had a marked loathing for the male genitalia. We did not refer her to a psychiatric clinic but decided to wait until the infant was born and observe whether or not there would be some sort of spontaneous adjustment in the event of a male child. It was a male child, but the mother seemed fond of her infant and nursed him. Nevertheless, on account of the prior obsession, discovered only after special questioning, we are going to follow up her emotional reactions in the postnatal clinic and refer her in the event that it seems necessary, since no physical complications exist.

Case 3.—Mrs. J. M., white, aged 24, had no previous history of emotional upset. Home situation moderately good. In the eighth month of her pregnancy she stated that she had marked phobias concerning the event of childbirth, believing that "something terrible was going to happen." She had insomnia and marked tremors of her hands and legs. During the ninth month of her pregnancy the nervousness seemed somewhat better, but greatly increased by the birth of a deformed infant showing congenital absence of the abdominal wall followed by death on the third day. Mrs. J. M. now believes that she had special knowledge of the event before it happened, and that her intuitive feelings about things will predestinate their occurrence. We will observe her carefully and refer her to psychiatric clinic at a later date if she does not get rid of this delusion.

Conclusions. 1. So-called "normal pregnant women" might well be highly abnormal, and even if they are not they are anxious to a degree beyond that of the so-called "normal" non-pregnant female.

2. Types of anxiety are influenced by the social and economic group from which they are selected.

3. In the group of 50 cases adequately followed up after childbirth, even though the economic situation was unchanged, there was a definite lessening of anxiety in 40 cases.

4. We make a plea for at least one experienced "dispensary" staff attendant at each prenatal clinic, and for a note of the nervous status on each obstetrical record.

5. All women showing phobias or even marked anxiety during

pregnancy should receive sympathetic encouragement by the chief of service, and if necessary, psychiatric advice.

6. Among 100 presumably normal pregnant women 75% showed anxiety related to economic stress; 7% to their husbands, 10% to other members of their families; while 16% showed definite phobias concerned with fear of ill-health or death, or of the child being defective.

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PNEUMOCOCCUS MENINGITIS WITH RECOVERY.

A Report of Three Cases.

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Recovery from pneumococcus meningitis is a very rare occurrence. Since Bedell's cases (3) in 1934, occasional reports are found in the literature; but several of these are not proven cases of pneumococcus infection, from the laboratory evidence presented. The use of sulphanilamide has been advocated in certain pneumococcal infections. The gratifying results obtained in these cases suggests the efficacy of this drug in the treatment of such cases and has prompted us to report the 3 cases in detail.

Case Reports. Case 1.—J. H. C., Jr., a student, aged 16, was admitted to this hospital under the care of one of us (W. B. A.), on the evening of July 23, 1937. The complaint at that time was of headache and fever. The family history was quite irrelevant. The past history was strikingly negative except for the usual childhood diseases and a tonsillectomy in 1935.

He was in excellent health until June 14, 1937, when he was in an automobile accident and was thrown clear of the car. This resulted in the fracture of his skull and right clavicle. He was unconscious for 1½ hours and was irrational for the 3 days after the accident. The fracture of the skull was in the right frontal region, involved the right frontal sinus and extended into the ethmoid sinuses at the base of the skull. From the onset, the vision in the right eye was greatly impaired, and this was thought to be due to the trauma. Convalescence seemed to be entirely satisfactory until July 6, 1937, when he developed a fever of 103° F. with chest pain and an unproductive cough. These symptoms were diagnosed as pneu-

monia and after a few days he became afebrile. However, on July 21, he again had a sudden rise in temperature to over 103° F., with a subsequent continuous fever ranging between 103° and 104° F. On July 22, he developed a stiff neck and became stuporous, and with this, vomiting was almost constant.

Examination. The boy was acutely ill, semicomatose, irritable and had obviously lost weight. The temperature was 104° F., pulse 132 per minute and the respirations were 24 per minute. The face was flushed. The skin was warm and dry, and no petechiæ or purpuric areas were seen. There was no edema. There was a small scar just below the left eyebrow which had the appearance of having been recently acquired. There were no gross skeletal abnormalities. The eyes were of interest: they were not prominent; the extra ocular movements were fairly well performed—save for inability to converge with the right eye; the conjunctivæ were injected. The right pupil was larger than the left and gave a paradoxical response to light. The left pupil reacted promptly to light and the right pupil gave a consensual response. The ocular fundi, save for rather pronounced pallor of the right disc, were thought to be normal. The ear drums were intact and there was no evidence of infection. There was a slight mucoid discharge from the nose. The pharynx was not remarkable. There was no glandular enlargement of note. The lungs were quite clear to percussion and auscultation. The heart was not enlarged and except for the tachycardia was considered normal. The blood pressure was 108/68. The abdomen was flat and no viscera or masses were palpable. The genitalia were of normal configuration and the rectal examination was not remarkable.

Examination of the central nervous system revealed that the cranial nerves were intact with exception of partial impairment of the optic nerve on the right. No motor or sensory changes were discovered, except for general hyperesthesia. The deep reflexes were present and very active. The superficial reflexes were normal in response and there were no abnormal reflexes elicited. There was marked stiffness of the neck with positive Brudzinski and Kernig signs.

The blood count showed: Hemoglobin, 13 gm. (90%); erythrocytes, 4,830,000; leukocytes, 36,500 with adult and juvenile neutrophils forming 90% of the total count. The blood Wassermann reaction was negative. The urine was acid with a specific gravity of 1.022. There was but a slight trace of albumin and no sugar was present. No formed elements were present. The urine culture was sterile. The blood chemistry revealed a fasting sugar of 91 mg. %; and non-protein nitrogen of 20 mg. %.

Roentgen ray examination of the chest showed the lungs to be clear; those of the head revealed evidences of an old fracture in the right frontal region involving the right frontal sinus and extending to the base of the skull; those of the sinuses showed an old fracture of the right frontal bone which extended into the right frontal sinus, and clouding of the right ethmoids and right antrum; those of the orbits did not reveal any evidence of osteomyelitis.

The blood cultures were sterile.

The first specimen of cerebrospinal fluid was obtained under an increased pressure and the Queckenstedt was negative. The fluid was opalescent and contained 22,500 cells per c.mm. The differential count showed 93% neutrophils and 7% lymphocytes. The stained smear showed a few organisms and the morphology of these suggested pneumococci. The cultures revealed a bile-soluble organism identified as a pneumococcus (Type XIV).

Treatment. It was thought advisable to institute drainage by repeated lumbar punctures. However, with the striking improvement in the patient's condition within the first 36 hours, this procedure was only done to deter-

mine the cell count and obtain cultures. It was not necessary to do a lumbar puncture to relieve the symptoms of pressure at any time after the first 36 hours. When the causal organism was definitely identified, sulphanilamide therapy was begun immediately. During the first 24 hours he received 2.4 gm. of the drug by mouth. During the subsequent 4 days he received 4.8 gm. by mouth per day. On the fifth day this was increased to 5 gm. in the 24 hours and in the following 24 hours he received 6 gm. of sulphanilamide by mouth. Finally on the ninth day of hospitalization, or the eleventh day of the acute illness, the drug was stopped after the patient had received 3 gm. and no further therapy was employed.

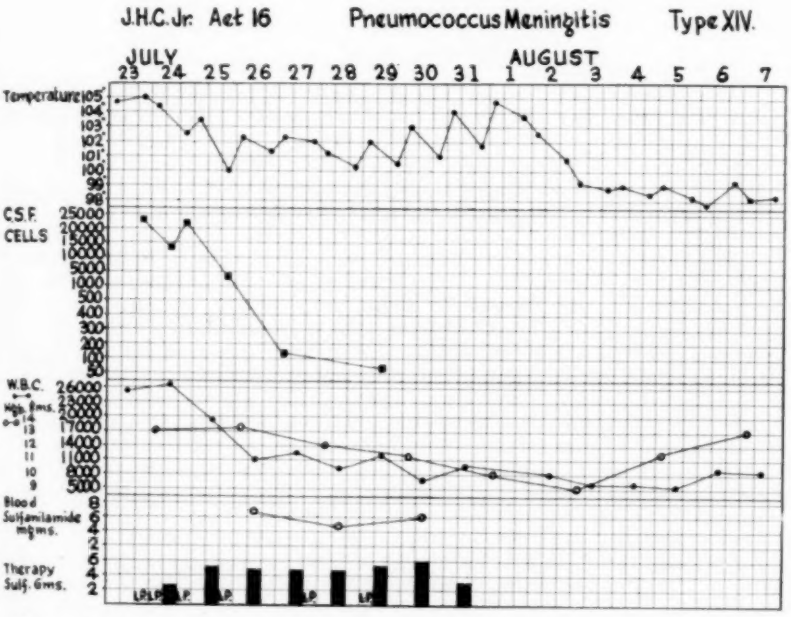

CHART 1.—Case 1. J. H. C., Jr., male, aged 16, meningitis due to pneumococcus Type XIV.

Course. The temperature continued high for the first 36 hours after admission and gradually fell but did not become normal. After the third day of sulphanilamide therapy the temperature gradually rose until it reached 105° F. by the eighth day of treatment. We felt that, with the clinical improvement, we were justified in assuming that the elevation in temperature was due to the drug used; therefore, the administration of sulphanilamide was discontinued. It was gratifying to find that the temperature fell rapidly to normal in the next 24 to 36 hours and remained so during the remainder of the patient's hospital stay. It is of interest that sulphanilamide had no deleterious effects on the cells of the blood.

The cerebrospinal fluid cell count was high on the first 3 occasions and it fell rapidly. With the fall in this cell count there was a gradual change noted in the types of the cells. At first, practically all were neutrophils and latterly the mononuclear elements predominate. The organisms were scanty in the bacterial smears. The number of organisms on culture was not abundant, and the culture taken 48 hours after admission was sterile.

The subsequent cultures were likewise sterile. Sulphanilamide had been given over a period of some 36 hours before the first sterile culture was obtained. The blood sulphanilamide level at this time was 6.7 mg. per 100 cc. of blood. Unfortunately, we do not know the sulphanilamide level in the spinal fluid as such determinations were not being done at that time.

The improvement in the patient was most dramatic; the pertinent data are collected in the appended chart.

A very curious and perplexing feature occurred on the day after admission when the left upper eyelid was found to be edematous. The edema became more marked and a definite swelling was noted in the periorbital tissues, resulting in slight proptosis of that eye. It was our feeling that he probably had a periorbital abscess. This was treated with hot compresses and with the general improvement in the patient the swelling subsided, so that no surgical intervention was necessary. At the time of discharge there was no residuum of this swelling.

In a recent communication from the patient he states that he is feeling very well, has gained weight and is not experiencing any untoward effects from his illness.

Case 2.—F. T., a salesman, aged 42, was admitted to this hospital under the care of Dr. Walter Dandy, on December 20, 1937. The complaint was severe occipital headache, and he was seen by one of us (W. B. A.) at Dr. Dandy's request.

The history is very interesting and dates back to early in 1935. The patient's first complaint was progressive deafness with tinnitus in the right ear and a unilateral headache on that side. There was no associated vertigo or vomiting. For these complaints he was admitted to the neurosurgical service on April 26, 1937. The findings were essentially negative but the audiometer tests pointed to an acoustic nerve tumor on the right side.

On April 27, 1937, a neurinoma weighing 10.5 gm. was removed. The subsequent postoperative course was very satisfactory so that on May 7 a spinofacial anastomosis was done. Dr. Dandy described a leak of clear cerebrospinal fluid that filled the wound several times and no site for the leak was found. Following this operation the patient had a moderate rhinorrhea. The wound was again explored on May 17, and in Dr. Dandy's words: "The rhinorrhea in this case is most unusual. It must come from the operative field because there never has been any before . . . . The wound was opened partially and the angle was thoroughly inspected. It was perfectly clear. There was no hematoma and the defect looked about as it did at the time of operation. We tried to place a piece of muscle in the porus acusticus, but it would not stick and wax would not stick either." Repeated efforts were made to scarify and obstruct the right Eustachian tube without any satisfactory result.

The rhinorrhea persisted and further efforts were made by Dr. S. J. Crowe and Dr. J. W. Baylor to occlude the right Eustachian tube by the local application of iodine. These attempts again proved unsuccessful. The rhinorrhea persisted and the patient was quite well until December 15, 1937. On this day, 1 hour after eating, he vomited and later developed a severe occipital headache. No bulging was noticed in the right cerebellar defect, nor was there any increase in the amount of cerebrospinal fluid discharge from the nose. After 24 hours the patient's neck became stiff and he developed a febrile reaction, the temperature rising on occasions to 103° F. He did not become delirious, lose consciousness or have convulsions. He was again admitted to Dr. Dandy's service with a temperature of 99.6° F., pulse of 86 and respirations of 14, on December 21.

Examination. The examination at the time of admission revealed a well-nourished man, who was very drowsy and who complained constantly of a severe occipital headache. There was no petechiæ. The skin was

warm and moist. The ocular fundi were quite normal. The rhinorrhea was noted, but it was no more marked than on the previous examinations. The lungs were quite clear. The cardiovascular system showed no abnormalities. The blood pressure was 132/68. The neurologic examination revealed a very marked stiff neck and a bilaterally positive Kernig. The defect in the cerebellar region was quite soft. There was a palsy of the seventh cranial nerve on the right, which was of the peripheral type, and the nerve had shown a marked return of function after the spinofacial anastomosis. The fifth cranial nerve was intact. There was no nystagmus, ataxia or staggering and the Romberg sign was negative.

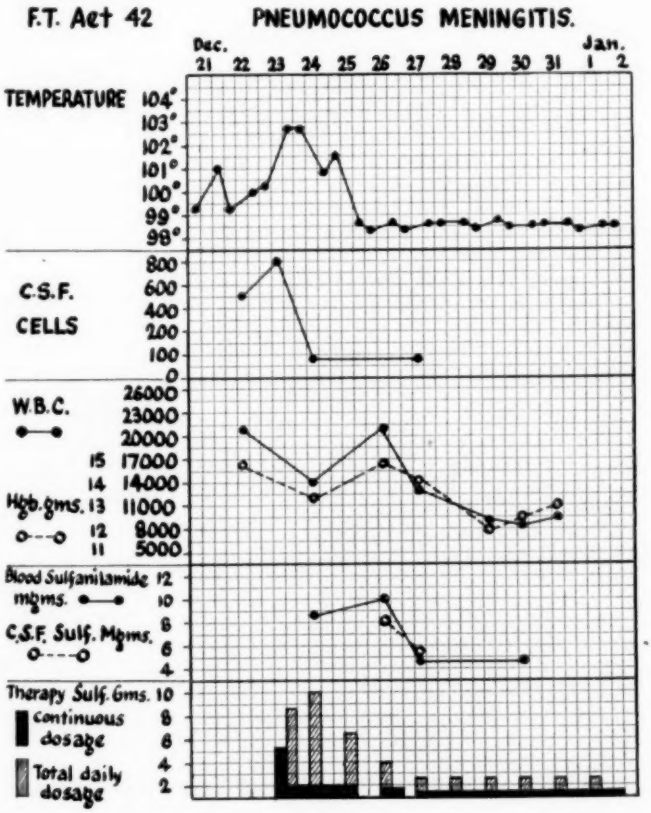

CHART 2.—Case 2. F. T., male, aged 42, meningitis due to pneumococcus Type XXIX.

It was felt that the patient had a meningitis due to a retrograde infection by way of the Eustachian tube, middle ear and mastoid cells.

The blood count showed: Hemoglobin, 102% and leukocytes 20,150 with a normal differential formula.

The urine was normal in every respect. The blood Wassermann reaction was negative. The blood cultures were sterile.

The first specimen of cerebrospinal fluid was obtained without any

increase in pressure and the Quekenstedt was negative. The fluid was opalescent and contained 500 cells, all of which were neutrophils. The stained smear did not reveal any organisms but the culture revealed a bile-soluble organism identified as a pneumococcus (Type XXIX).

Treatment. The treatment in this case was not directed at repeated lumbar puncture as there was no obvious increase in intracranial pressure. Because of the success attributed to sulphanilamide in Case 1, this was instituted on December 23 after the organism had been accurately identified. The patient received sulphanilamide by mouth only. He was given 5.3 gm. of sulphanilamide with sodium bicarbonate on the morning of December 23 and received 1.5 gm. every 4 hours during the remainder of that day and the following day. Through the day of December 25 he received 0.9 gm. every 4 hours, and from December 26 to January 2, 1938, he was given 0.6 gm. of sulphanilamide 4 times a day. Unfortunately, through some misunderstanding the sulphanilamide was discontinued through the nights of December 25 and 26 and we feel that this explains the low blood and cerebrospinal sulphanilamide levels on the morning of December 27.

Course. The day after treatment was instituted the patient's condition had improved. The headache was much less severe and had entirely disappeared by December 27. During the first 48 hours after treatment was commenced the rigidity of the neck became less and was entirely absent by December 26.

The temperature fall was dramatic as seen in Chart 2.

As in Case 1 no deleterious effects from the therapy were noted on the blood picture.

The culture of the spinal fluid was positive for Type XXIX pneumococcus before treatment and on the afternoon of the institution of therapy was still positive for the same organism. The subsequent cultures were sterile and the cell count fell from an original level of 500 to 80 cells.

It is very common to find cyanosis of varying intensity in individuals receiving sulphanilamide. The cyanosis in this case became marked, but in spite of continuing sulphanilamide it had entirely disappeared on December 31 (eighth day of therapy).

The patient was discharged on January 2 entirely recovered from the meningitis. At the time of writing he is in this hospital and Dr. Dandy has repaired the defect in the dura causing the leak, with gratifying results.

Case 3.—V. L. R., an 18-year-old negro, was admitted to Dr. W. T. Longcope's service of this hospital, on December 24, 1937, because of headache, fever and delirium of 3 days' duration.

The family history was irrelevant.

The past history was non-contributory, save for infrequent mild headaches several years previously. There had been no other symptoms of sinusitis, and no more than the usual one or two colds a year.

The present illness began 6 days before admission when the patient complained of frontal headache. There had been no previous upper respiratory infection. The headaches gradually became more severe, and 3 days before admission he began to feel feverish and developed a slight cough. There was occasional vomiting. He was delirious at times. There was an indefinite story of slight puffiness of the eyelids.

Examination. The patient was a well-nourished and well-developed young negro. He was restless and delirious. The temperature was 104° F., the pulse 112 and the respirations 32. The skin was hot and dry. No rash was seen. The right pupil was small, the left large; both reacted well to light. The fundi were normal. The ear drums were normal. No sinus or mastoid tenderness could be elicited. The tonsils were of moderate size. The pharynx was moderately injected, and there was a purulent postnasal

discharge. The lungs were clear, and the heart was not enlarged. The blood pressure was 120/70. The examination of the abdomen and genitalia was not remarkable. The deep reflexes could not be obtained. No abnormal reflexes were elicited. The cranial nerves were intact, and there were no gross motor or sensory changes. There was marked stiffness of the neck, and a positive Kernig sign.

The blood count showed: Hemoglobin, 13.8 gm. (94%); erythrocytes, 4,300,000; leukocytes, 12,300 with 90% neutrophils. The blood Wassermann reaction was negative. The urine was normal. The blood cultures, taken on the first and second days, were sterile.

Lumbar puncture revealed cloudy spinal fluid under a pressure of over 55 mm. of water. There was a normal jugular response. The cell count was 8000 per c.mm., with 70% neutrophils. The stained smear showed no organisms, and the patient was therefore given 10 cc. of the concentrated New York State antimeningococcus serum, intrathecally.

Sulphanilamide was begun, the dosage varying between 6 and 8 gm. a day. It was given subcutaneously in the form of an 0.8% solution with 1/6 molar sodium lactate, or by stomach tube with sodium bicarbonate.

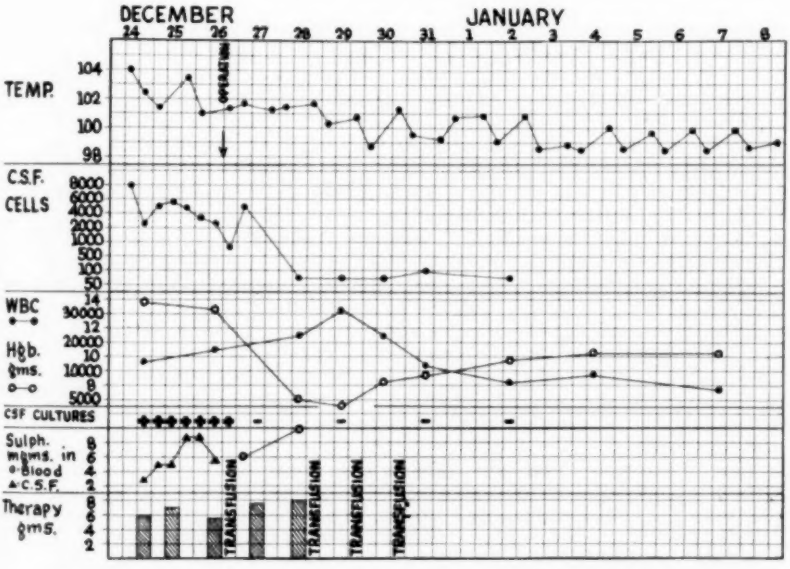

CHART 3.—Case 3. V. L. R., colored male, aged 18, meningitis due to pneumococcus Type XX.

Course. Lumbar punctures were done every 8 hours. Culture of the fluid obtained at the first 7 punctures all showed pneumococcus Type XX. At the second and third punctures antimeningococcus serum was given. After the nature of the organism was determined this was discontinued, and 10 cc. of 1% sulphanilamide was given, intrathecally, following drainage of the spinal fluid.

On the second hospital day his clinical condition was worse. He was extremely restless and combative. There was a divergent strabismus. The heart had apparently dilated, for the apical impulse had shifted to the anterior axillary line. There was a marked dicrotic wave in the pulse.

The blood pressure remained at 120/70. The spinal fluid sulphanilamide levels were 4.9, 4.8 and 8.4 mg. %.

On the third day the clinical condition was unchanged, save that the blood pressure had fallen to 90/50. Large amounts of sedatives were required to control the restlessness. The temperature had varied between 101° and 103.6° F. The hemoglobin was 90%. The leukocyte count had risen to 17,100. The spinal fluid cell counts were 3500 and 2500, with spinal fluid sulphanilamide levels at 8.5 and 5.6 mg. %. Cultures remained positive for pneumococcus Type XX. Sinus Roentgen rays were taken but were unsatisfactory, because it was impossible to hold the patient's head sufficiently still. Examination with a nasopharyngoscope, however, showed a purulent discharge coming from the orifice of the left frontal sinus.

Because there was no evidence of any other focus, a radical frontal operation under ether anesthesia was performed on the third hospital day by Dr. Samuel Crowe. A large quantity of pus was evacuated from both frontal sinuses. There was considerable erosion of bone in the anterior walls of the frontal sinuses, but no evidence of communication with the meninges through the posterior walls was found. Cultures of the pus from the sinuses showed pneumococcus Type XX.

Following operation the blood pressure fell to 82/44, and he was given a transfusion of 600 cc. and intravenous normal saline. On the following day (the fourth) his clinical condition was unchanged. The spinal fluid cell count was 5000, but the culture was sterile, as were all subsequent cultures and the 2 mice inoculated with the spinal fluid intraperitoneally survived. The blood sulphanilamide was only 5.9 mg. % and it was felt that the sulphanilamide given by stomach tube was probably not being adequately absorbed, so the subcutaneous method only was used thereafter. The urine on this day showed a trace of bile and a moderate amount of urobilin. The scleræ were faintly icteric.

On the fifth day the blood sulphanilamide level had arisen to 10.7 mg. %. The hemoglobin had fallen to 48%, and the leukocyte count had risen to 22,000. The urine contained a large amount of urobilin. Sulphanilamide was therefore discontinued, and the patient given a transfusion of 600 cc.

There was evidence of some clinical improvement. The left border of the heart had returned to its former position, 8 cm. to the left of the midsternal line. The blood pressure has risen to 120/70, and the dicrotic wave in the pulse had disappeared. At times, the patient would respond slightly to commands. There was, however, some blurring of the nasal margins of the optic discs.

Several attempts at lumbar puncture were unsatisfactory, because of the extreme restlessness of the patient despite large amounts of sedatives. Because it was deemed imperative to determine whether or not a block had occurred, a 16-gauge needle was inserted in the lumbar region under ether anesthesia. Following bilateral jugular compression 300 cc. of almost clear fluid was obtained. The cell count was only 80. The needle was then filed off 1 cm. from the skin and left in place.

On the sixth day he was much improved, and able to take fluids by mouth. Spinal fluid was draining freely from the needle. The hemoglobin was 40%, the leukocyte count 32,000 and the serum bilirubin 3 mg. %. He was given a third transfusion.

Following this he continued to improve rapidly. On the eighth day the spinal needle was removed. The cell count had remained between 80 and 100 cells, 70% of which were neutrophils. The hemoglobin had risen to 68%. The leukocyte count had fallen to 12,300, and several nucleated red cells and 5.3% reticulocytes were present in the blood smear. Urobilin had disappeared from the urine. The operative wound was remarkably clean, but some purulent discharge continued to be present in the nasopharynx.

TABLE 1.—OTHER CASES OF PNEUMOCOCCIC MENINGITIS REPORTED SINCE 1934.

Ref. No.	Sex.	Age.	Onset.	Cell count of original cerebrospinal fluid.	Identification of organism.	Treatment.
1	F	9	Two days following pneumonia	1600 per c.mm.; mostly polys.	No organism seen in smear or culture	None.
2	F	9	Otitis media; chronic mastoiditis	2000 per c.mm.	Pneumococcus Type V	Antimeningococcus serum; transfusion; sulphanilamide—intraven., intraspin., intramus., subcutan.
3	F	42	Four days after onset of acute sinusitis	8000 per c.mm.; polys., 88%	Organism identified in smear and culture, pneumococcus Type IV	Continuous cisternal drainage and cisternal irrigations.
4	F	9	Otitis media with recrudescence	1686 per c.mm.; polys., 88% 2. 2050 per c.mm.	No organism in the smear or culture originally Organisms in smear and culture Gram diplococci with capsules and in short chains; not typed	Spinal drainage; transfusions.
5	M	29	"Primary" ?	No statement	Cultures said to have confirmed	No treatment; ? "spontaneous."
6	F	25	Six days after tonsillectomy	540 per c.mm.; polys., 85%; lymphos., 15%	Organism in smear and culture; not typed	Antimeningococcus and antipneumococcus sera; mercurochrome by vein.
8	?	5	"Primary" ?	3500 per c.mm.	Gram diplococcus by smear and culture; short chain streptococcus	Cisternal drainage; antimeningococcus serum, small amount.
9	?	?	Mastoiditis	No details	Pneumococcus Type V	Prontylin—tabs. 1 g. 4 h. for 7 days—no effect, discontinued optochin was used throughout.
10*	?	?	After tonsillectomy and ethmoid op.	?	Stated Type XXXI	Sulphanilamide.
	?	?	48 hrs. after submucous resection and turbinate op.	?	Stated Type XXIX	Sulphanilamide.
	?	?	After double otitis media and double mastoiditis	?	Stated Type IV	Sulphanilamide.
11	M	59	Chronic otitis media and mastoiditis	18,600 per c.mm.; almost all polys.	Organism in smear and cultures; not typed	"Spontaneous;" symptomatic.
12	F	12 days	...	...	Organism in smear	"Spontaneous."
13	F	20	History of sinusitis; head injury	2420 per c.mm.	Organism in culture agglutinated in sera of Types I and II	Felton's serum by vein, cistern and subarachnoid space; glucose, 50%, by vein; $MgSO_4$, 33% by rectum.
14	F	43	Mild "cold" 2 weeks before	1060 per c.mm.; numerous erythrocytes	Organisms seen only in smears	Felton's serum, Types I and II.
15	F	7	7 wks. after a purulent otitis media	150 per c.mm.; polys., 80%	Pneumococcus Type III by culture	Spinal and cisternal drainage; antimeningococcus serum.
16	M	28	Head injury; C.S.F. from nose	Fluid cloudy—no cell count; polys., 100%	Pneumococcus Type I	Felton's serum—intrav. and intrasp.

* This and the 2 following cases are recovered ones from a group of 14 cases of pneumococcic meningitis; 11 cases succumbed.

On the elventh day his temperature had fallen to normal, and aside from the operative wound, he was apparently perfectly well. He was discharged on January 23, 1928, after 32 days in the hospital.

Discussion. Pneumococcus meningitis is a relatively uncommon disease. In a review of such cases reported since 1934 (Table 1) we are impressed with the fact that the meningitis is most commonly secondary to an otitis media or sinusitis. This does not seem unusual inasmuch as the upper respiratory tract is a common habitat for the pneumococcus.

Meningitis as a complication of lobar pneumonia would seem quite rare from our review of the reported cases. This is quite in keeping with the generally accepted statistics. In large series[7] of cases of lobar pneumonia meningitis occurs as a complication in from 0.2 to 2.4% of all cases.

A striking feature in the tabulated cases from the literature is that the evidence in many is very inconclusive that the causal organism is the pneumococcus. This objection has been raised before. The organisms obtained in our 3 cases were identified in smears by Gram's stain. The cultures of the cerebrospinal fluid revealed typical bile-soluble organisms. The organisms were identified as Type XIV pneumococcus in Case 1; Type XXIX pneumococcus in Case 2; and Type XX pneumococcus in the last case. It seems beyond a doubt that we were dealing with pure pneumococcal infections. The organisms, in all 3 cases, though plentiful, were not found in overwhelming abundance in the spinal fluid.

The treatment in these cases was first directed at adequate drainage of the subarachnoid space. This played an appreciable rôle in the third case. A search for an apparent source of organisms in the mastoid and paranasal sinuses is of vital importance, and such a focus should be completely removed. It is apparent from Chart 3 and from the clinical description of that patient, that there was no improvement in the third case prior to the operation. Within 16 hours after the operation, however, the organisms had disappeared from the spinal fluid, and after 48 hours the spinal fluid cell count had dropped to 80, and clinical improvement had begun. Certainly the removal of the focus of infection which presumably was feeding organisms into the spinal fluid was a major factor in recovery in this case. No like focus could be identified in the first 2 cases, though it was strongly suspected in the first.

No toxic effects from the administration of the sulphanilamide were noticed in the first 2 cases other than moderate cyanosis in Case 2, and a moderate febrile reaction in Case 1.

The marked hemolytic anemia observed in the third case has been commented upon in other instances. It was quite severe in this case and it was necessary to give blood transfusions.

No specific antipneumococcus serum was used.

The sulphanilamide was given orally in all the cases and, in addi-

tion, it was given intrathecally and subcutaneously in the third case. Whether this patient would have survived without the additional use of sulphanilamide is a matter of conjecture. However, we feel reasonably certain that this drug was responsible for recovery in the first 2 cases. In 1 of the cases recently reported by Basman and Perley[2] a similar beneficial effect is shown.

Summary. Three cases of pneumococcus meningitis are reported. The organism was definitely a pneumococcus and the types were XIV, XXIX and XX respectively. The beneficial effects of sulphanilamide alone in Cases 1 and 2; and, with other procedures in Case 3, are demonstrated.

We are indebted to Dr. Perrin Long for his helpful guidance in the preparation of this report.

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BOOK REVIEWS AND NOTICES

TISSUE REACTIONS IN BONE AND DENTINE. A morphobiological study of the formation and the dissolving of bone and dentine. By ÅKE WILTON, M.D., Assistant Professor and Lecturer in Pathology at the Caroline Institute, Stockholm. Pp. 194; 64 illustrations and 5 plates in color. London: Henry Kimpton, 1937. Price, 15/.

THE book contains a summary of the results of the studies of the author on bone and dentine. In the first part the author discusses osteogenesis and dentinogenesis. The conclusion is drawn that the maturity of the matrix depends on the differentiation of the bone and dentine forming cells. Cells of low differentiation form but an immature matrix, which is transformed into mature matrix only after the cells have been fully differentiated. Though differentiation and proliferation usually appear to be antagonistic, under certain conditions as in rachitis or achondroplasia, a factor (N-factor) makes its appearance, which brings about an abnormally slow differentiation with a simultaneous decrease in proliferation (N-reaction).

In the second part of the book the author presents his findings on osteolysis and dentinolysis. He distinguishes: 1, active bone resorption occurring in young bone, which is characterized by unmasking and dedifferentiation of the osteocytes, which again proliferate and transform into other cells. This resorption has been observed by the author in experimental osteolysis by parathormone, Paget's disease, scurvy and osteogenesis imperfecta; 2, passive bone resorption, in older bone the osteocytes of which have lost the ability of dedifferentiation. This resorption is accomplished by reticuloendothelial cells; 3, lingering bone resorption which is interpreted as physiologic dedifferentiation of bone cells not accompanied by proliferation of osteocytes. The author believes that the alterations in scurvy and osteogenesis imperfecta are produced by a factor (W-factor) which brings about abnormal dedifferentiation with abnormal increase in growth (W-reaction). The N- and W- factors have, however, nothing to do with the real genesis of the diseases. Although the description and pictures given by the author did not convince the reader of the soundness of his deductions, the book certainly must be regarded as valuable and should be thoroughly studied by the student of bone diseases. W. E.

CLINICAL URINALYSIS AND ITS INTERPRETATION. By ROBERT A. KILDUFFE, A.M., M.D., F.A.S.C.P., Director of Laboratories, Atlantic City Hospital; Pathologist, Atlantic County Hospital for Tuberculous Diseases, etc. Pp. 428; 40 illustrations. Philadelphia: F. A. Davis Co., 1937.

DR. KILDUFFE here brings out an easily readable book for the practitioner to use in his office, but insufficient in detail for the beginning medical student and too clinical in its interpretation for the laboratory technician. He enumerates and describes methods of distinct value that can be performed in a small office laboratory and discusses the interpretation of such examinations for the physician. He covers many tests in the book but does not specify the reaction, either physical or chemical, that makes the test possible. Even the busy practitioner in his leisure moments might like to know why certain reagents are needed in the performance of an analysis. An addition of this sort would not be too long. Many of the procedures give a presump-

tive result but when greater accuracy is needed additional tests are set forth. An excellent feature is the enumeration of certain fallacies that modify the interpretation of the results obtained in various analyses.

In the introduction the present concepts of urinary physiology are briefly but thoroughly considered to give a basis for later evaluations of laboratory findings.

A chapter is devoted to the collection and preservation of urine for various analyses. As so many specimens are collected and preserved improperly, this section is of great value to the office assistant.

The somewhat involved mathematical calculations necessary in determining renal functional tests are simplified as much as feasible. Exact instructions as to methods for performing the tests from the injection of test substances to the calculations of the results are set forth. This chapter is what many physicians have long sought for.

A brief section is devoted to the endocrine aspects of the urine and the methods of pregnancy diagnosis are enumerated. A discussion of the accuracy of the tests and applications in conditions other than pregnancy is included and is quite satisfactory for the practitioner. No bacteriologic methods of urine examination are given but presumptive methods such as smears are presented. This is frequently sufficient in the office laboratory. There are a number of errors in proof reading that are easily picked up.

H. F.

NEUERE ERGEBNISSE AUF DEM GEBIETE DER KREBSKRANKHEITEN. Fortbildungskurs der Berliner Akademie für ärztliche Fortbildung (vom 19. bis 26, Oktober, 1936). Herausgegeben von PROF. DR. C. ADAM und PROF. DR. AULER. Forty-four Contributors. Mit einem Vorwort von GEHEIMRAT PROF. DR. BORST, München. Pp. 366; illustrated. Leipzig: S. Hirzel, 1937. Price, Paper, Rm. 12; Bound, Rm. 13.50.

THIS book is based upon a series of lectures delivered by 47 specialists in oncology. The aim of these lectures was to present to practicing physicians a survey upon the more important phases of cancer research, and particularly, to discuss the newer advances made.

A great variety of subjects are covered. There are lectures on the significance of the experimental study of cancer, the etiologic relation of virus to cancer, the factors of heredity and race, and many other problems of like interest. Two chapters deal with the occurrence of tumors among domestic animals, and in plants. About half of the book is devoted to subjects of more specialized interest, such as carcinoma of the stomach, the lungs, the skin, the intestines, and of various other organs. Finally there are chapters on treatment with surgery, Roentgen rays and by other agents. To many of the lectures an excellent bibliography is appended.

The book is good as a survey, but it is in no sense a systematic textbook. With the present day interest in cancer, a collection of lectures such as this is welcome and fulfills a useful purpose.

B. L.

APPLIED PHARMACOLOGY. By A. J. CLARK, M.C., M.D., F.R.C.P., F.R.S., Professor of Materia Medica and Pharmacology in the University of Edinburgh, etc. Pp. 678; 84 illustrations. Sixth edition. Philadelphia: P. Blakiston's Son & Co., Inc., 1938. Price, $5.00.

FOR this edition the book has been rearranged and a considerable amount of new material dealing with hormones, vitamines, and chemical transmitters has been added. Considering its relatively small size, the amount of information is surprising, and this is particularly true of the résumés of the

physiology of the various body systems which precede discussions of the actions of drugs upon them. In some respects, notably the biochemistry of drug actions, this book is so modern as to be ahead of its time, affording a glimpse of what the pharmacology of the future may look like; in other respects it is behind the times. This is to be expected, since one of its chief merits is brevity achieved by selection of material which the author deems most valuable. For a complete presentation of all the available facts other books must be consulted. The book deserves high recommendation for the physician and student as a stimulating, modern presentation of the existing physiologic and biochemical basis for therapeutics.

C. S.

ERBKRANKHEIT UND FERTILITÄT. Mikropathologie der Spermien erbkranker Männer. von DR. MED. ET MED. VET. H. STIASNY, Assistent der chirurgischen Abteilung des städtischen Krankenhauses "Am Urban," Berlin, und DR. MED. K. D. J. GENERALES, JR., Lowell, Mass. z. Zt. Volontärassistent der chirurgischen Abteilung des städtischen Krankenhauses "Am Urban," Berlin, Mit einem Geleitwort von PROF. DR. ERWIN GOHRBANDT. Pp. 163; 60 illustrations, 21 tables (16 in colors). Stuttgart: Ferdinand Enke, 1937. Price, Paper, Rm. 27.; Bound, Rm. 29.

THE authors have availed themselves of the extraordinary clinical opportunity resulting from the German law of July 14, 1933, to study the correlation between fertility and heritable disease. Their attention has been directed principally to the morphology of the spermatozoa. In healthy fertile men it was found that 19% of the spermatozoa could be classified as morphologically abnormal; in men suffering from inheritable disease it averaged that 63.85% of the spermatozoa were abnormal. Actual figures ranged from 75.1% abnormality in chronic alcoholism to 53.8% in schizophrenia. It was impossible, however, to correlate the type or degree of abnormality to any specific heritable disease. This very excellent monograph is profusely illustrated with microphotographs and colored drawings of the various types of abnormal spermatozoa.

B. H.

FEARFULLY AND WONDERFULLY MADE. The Human Organism in the Light of Modern Science. By RENÉE VON EULENBURG-WIERNER. Pp. 472; 17 illustrations. New York: The Macmillan Company, 1938. Price, $3.50.

THIS book attempts in a brief compass to express for the layman or the elementary student the basic facts of life. This difficult task has been admirably achieved. The facts are simply stated without undue use of technical terms; where technical terms are employed they are adequately explained. The ground is covered in an amazingly small number of pages, but in spite of this there is so much detail that the average physiologist will learn much that he has not previously known. The information given is amazingly accurate, considering the scope of the book. The layman should find it of great interest, even that part which may prove not completely intelligible owing to its complexity. Students of biology entering this field will find the statements clear and concise, but giving many facts for digestion and later assimilation.

However, the outstanding contribution of the book is the author's point of view. Looking at biology from the detached viewpoint of the philosopher, she regards physiologic statements as being made in terms of matter which probably does not exist in the concrete form which we commonly

attribute to it. She quotes Eddington's statement that if one could condense the protons and electrons that constitute the average adult body to a perfect solid, the mass would be just barely visible by the use of a microscope. She regards therefore the materialistic conceptions of the physiologist as mere conventions used to express partial knowledge of very complex situations. She says "Man cannot penetrate beyond the image of his mind, beyond the manifestation of energy which he himself is." The layman or the student commencing the study of biology cannot remember too often that the statements that he learns are only partially true. Any biologist or other scientist would be wise also to remind himself frequently of this fact. The book should be of much value to many different types of readers.

H. B.

GENITAL ABNORMALITIES, HERMAPHRODITISM, AND RELATED ADRENAL DISEASES. By HUGH HAMPTON YOUNG, M.A., M.D., Sc.D., F.R.C.S.I., D.S.M., Professor of Urology, The Johns Hopkins University; Visiting Urologist, Brady Urological Institute, The Johns Hopkins Hospital. Pp. 649; 379 illustrations, containing 534 drawings by WILLIAM P. DIDUSCH. Baltimore: The Williams & Wilkins Company, 1937. Price, $10.00.

APHRODITE, as a result of a celestial union with Hermes, brought forth an extraordinary child, one endowed with the attributes of both father and mother. Unable to determine the sex, they decided to affix both their names, and their child has gone down in history as Hermaphroditos. After this picturesque and mythical origin, these unfortunates have suffered cruelly from the advancing standards of morals and have found scant comfort from the attentions of lawmakers, historians, mythologists, poets, sculptors, painters and physicians.

The author of this unique monograph intended originally to present a group of remarkable genital abnormalities which he had encountered and treated surgically; but both interest in the subject and scope of opportunity grew, unfolding unexpected and hitherto undescribed conditions—anatomic, pathologic, endocrine and psychologic—which were intimately associated with each clinical problem. This large and well-illustrated volume presents his trials and successes with 55 cases of the most extraordinary examples of embryologic dysfunction and congenital abnormality that have ever been assembled. Divided into 22 chapters, the material ranges from the simple cases of hypospadias and epispadias (with depiction of the author's original and successful operative corrections) through his 17 cases of pseudohermaphroditism to culminate in the addition of the twentieth proven case, in the world's literature, of hermaphroditismus verus. Likewise are incorporated his 6 cases of adrenalectomy and a complete discussion of the adrenal-genital syndrome. Perhaps the most outstanding feature is the excellent result of the combination of the author's exquisite surgical technique and the artist's ability to depict the operative steps by his brilliant illustrations. It is a unique and an intensely human document, which lends a promise of a happier future to these unfortunate social pariahs.

A. R.

THE NEGRO'S STRUGGLE FOR SURVIVAL. A Study of Human Ecology. By S. J. HOLMES, Professor of Zoölogy in the University of California. Pp. 296; 10 illustrations and 50 tables, also appendix of 31 tables. Berkeley, Calif: University of California Press, 1937. Price, $3.00.

THIS monograph deals with a subject which has stimulated much speculation, but little of scientific value, dealing directly with the whole subject, has been contributed. "The biological trend of the American negro cannot

fail to have an important influence upon the people of the United States in many ways," as the author states.

He has made a thorough study of the problem of the survival of the negro from the biologist's point of view and collected much material bearing on the interracial struggle for existence between the white and colored races in this country. The factors influencing the growth and the limitations of the negro race, the effects of negro migration, of interbreeding with the white race and other biologic phenomena observable in the negro race are discussed. The interpretation of all the interacting factors and the ultimate outcome of the complex biologic problems which the coëxistence of the two races creates cannot be foretold. The author has, as he says, been brought face to face with a number of uncertainties which allows only a discussion of possibilities which may influence future national policies. No one can say what the ultimate fate of the negro in America is to be. This book is a scholarly analysis of the problem, and contains much material derived from the field of medicine regarding the relative effects of disease on the white and colored races.

G. R.

THE BIOLOGY OF PNEUMOCOCCUS. The Bacteriological, Biochemical, and Immunological Characters and Activities of Diplococcus Pneumoniæ. By BENJAMIN WHITE, PH.D., with the collaboration of ELLIOTT STIRLING ROBINSON, M.D., PH.D., and LAVERNE ALMON BARNES, PH.D. Pp. 799; illustrated. New York: The Commonwealth Fund, 1938. Price, $4.50.

A MONOGRAPH on the pneumococcus is opportune at a time like the present, when the attention of the public is being attracted to the pneumococcus and pneumococcal pneumonia. This book fills a considerable want. The completeness with which the author has treated such phases of the pneumococcus as its history, biochemistry, dissociation, pathogenicity, chemical constitution, specific polysaccharide-splitting enzymes, antigenicity, immunology, chemotherapy, production of antipneumococci serum and the serum treatment of lobar pneumonia makes the book valuable to the student, teacher, laboratory worker and clinician; in fact, valuable to almost anybody with a more-than-average interest in science or medicine. The research worker, no matter what phase of the pneumococcus he may be investigating, has here a valuable aid. The appendix, containing methods for preparation of the more important media, isolation and type determination of the pneumococcus, preparation of bacterial enzymes capable of decomposing capsular polysaccharides, serologic reactions and directions for the production and testing of diagnostic and therapeutic antipneumococcic serum, makes the book a valuable reference work in any laboratory. The bibliography of 1593 articles gives some idea of the thoroughness of the book and its potential value to any user.

H. M.

DIGESTIVE TRACT PAIN. Diagnosis and Treatment, Experimental Observations. By CHESTER M. JONES, M.D., Assistant Professor of Medicine, Harvard University; Physician, Massachusetts General Hospital. Pp. 152; 5 illustrations. New York: The Macmillan Company, 1938. Price, $2.50.

THIS brief monograph deals with the type and location of pain which follows distention of various portions of the gastro-intestinal tract. It is based on a series of careful experiments in which a balloon attached to the distal end of a rubber tube was introduced, under the fluoroscope, to any desired region from esophagus to rectum and then distended until

pain was produced. The character and location of the pain was carefully observed. The results are epitomized in a series of clear diagrams. The latter chapters consist of brief abstracts of clinical cases in which especial attention is directed toward localization of gastro-intestinal lesions, using as a guide the data obtained from the experimental study. Their intensely practical value becomes apparent when one observes that careful analysis of the nature and location of digestive tract pain is in itself often as diagnostically informing as more elaborate and costly study. The author is to be commended both on the content of the monograph and on its brief, direct presentation. K. E.

FRACTURES AND DISLOCATIONS FOR PRACTITIONERS. By EDWIN O. GECKELER, M.D., Fellow of the American College of Surgeons; Fellow of the American Academy of Orthopædic Surgeons. Pp. 252; 213 illustrations. Baltimore: William Wood & Co., 1937. Price, $4.00.

THE author states that the purpose of the book is to condense the subject of fractures and dislocations without the omission of important details. This little volume has 32 chapters and a short bibliography at the end of each chapter. Some of the sections are so short that they might well have been excluded. The material dealing with bone repair is totally inadequate for even a fair knowledge of the process. Without any preliminary explanation, the statement is made that "It is well known that phosphatase is found in large quantities at the site of fractures." There are numerous similar instances in the text. Although the volume is intended in large part for use by general practitioners such subjects as subcutaneous leverage, transfixion and even open reduction are discussed. The dangers of attempting to do this in so small a volume are self-evident. There is, however, much in this little volume which will be of interest to general practitioners. The sections on roentgenograms and the medico-legal aspects of fractures are good.

The work will be of value to students who wish rapidly to review the subject and to practitioners who want a small ready reference volume. Many of the fractures discussed such as fractures of the vertebræ, pelvis, humerus, femur, etc., are best treated by men who have had special training in fracture work and who have affiliations which permit of hospitalization. From this viewpoint, if the book was even in part intended for surgeons interested in fractures the volume is much like a compendium. The illustrations are good, and the type and paper excellent. The index is complete. I. R.

THE RÔLE OF CHEMIOTAXIS IN BONE GROWTH. By A. P. BERTWISTLE, M.B., CH.B., F.R.C.S. (EDIN.). Pp. 59; 32 illustrations. London: Henry Kimpton, 1937. Price, 8/6.

THIS monograph, by a British roentgenologist, deals with normal and pathologic bone growth. A law is propounded "that whenever young fibrous tissues, particularly young blood-vessels, come into contact with bone or a calcified deposit, new bone formation occurs." The fibrous tissue growth contacts the bone or calcium deposits as a result of "disruptive chemotaxis." The term "disruptive chemotaxis" is defined as "the power of certain hard substances of attracting and drawing into themselves certain soft, living substances." The thesis is interesting, not entirely new, and certainly not proven by the author, who is handicapped by thinking in terms of the gross pathology of the roentgenologist rather than in the terms of the cellular changes of the pathologist. G. W.

PRIMARY CARCINOMA OF THE LUNG. By EDWIN J. SIMONS, M.D., Member of the Staff, St. Gabriel's Hospital, Little Falls, Minn., and Lymanhurst Health Center, Minneapolis, Minn.; Visiting Consultant in Medicine, Minnesota State Sanatorium, Ah-gwah-ching, Minn. Pp. 263; 30 illustrations and 1 colored plate. Chicago: The Year Book Publishers, Inc., 1937. Price, $5.00.

THIS small monograph on primary carcinoma of the lung was written by a general practitioner for general practitioners. It will, however, prove of interest to internists, surgeons, roentgenologists and pathologists. The historical aspects and incidence in this and other countries, the etiology and pathology of the condition are carefully covered, though it is pre-eminently clinical in its approach. Diagnostic methods which can be used by the general practitioner or specialist, and differential diagnosis are fully reviewed. Sputum and pleural fluid examination is described and the use of bronchoscopy as a diagnostic aid is included. The various methods of therapy are comprehensively covered; symptomatic treatment, radiation, bronchoscopic treatment and surgery. More than 5000 proven cases of pulmonary cancer are analyzed. The bibliography includes approximately 500 papers. In the preparation of the work the author had had the advice of Wangensteen, Rienhoff and Graham, and has drawn freely from the works of leaders in the field of pulmonary diseases.

The illustrations are excellent. It is, I believe, the best available short monograph on the subject. It can well be compared with Alexander's monograph on the *Surgery of Pulmonary Tuberculosis*, written some years ago. Here is a volume that should find a place in the library of many physicians and specialists. They will all be wiser for having read it.

I. R.

SYNOPSIS OF DIGESTIVE DISEASES. By JOHN L. KANTOR, PH.D., M.D., Associate in Medicine, Columbia University; Gastroenterologist and Associate Roentgenologist, Montefiore Hospital for Chronic Diseases, New York. Pp. 302; 40 illustrations. St. Louis: The C. V. Mosby Company, 1937. Price, $3.50.

THIS small volume is divided into 4 sections, dealing with: 1, Such general considerations as diagnostic and therapeutic methods, functional and allergic disturbances of the gastro-intestinal tract; 2, a systematic description of digestive disease from mouth to anus; 3, diseases due to intestinal parasites; and 4, digestive symptoms of extradigestive disease. It is obvious that the synoptic treatment of such a vast field requires a brevity which is at one time a boon to the student and busy practitioner, and a strict limitation of the usefulness of the volume. The author's wide experience makes him well qualified to condense the material into a practical compend. Its only shortcomings are inherent in the very nature of an epitome rather than in the selection and presentation of its contents.

K. E.

EXTERNAL DISEASES OF THE EYE. By DONALD T. ATKINSON, M.D., F.A.C.S., Consulting Ophthalmologist of the Santa Rosa Infirmary and the Nix Hospital, San Antonio, Texas; Fellow of the American Academy of Ophthalmology and Oto-Laryngology. Pp. 718; 494 illustrations. Second edition, thoroughly revised. Philadelphia: Lea & Febiger, 1937. Price, $8.00.

THIS book deals with those conditions of the eye which do not require elaborate equipment for diagnosis. There are no recent publications in English covering only this field. However, the author has included in this

edition brief reference to slit lamp microscopy and to orthoptic training. The numerous illustrations, many from drawings or wax models by the author, are almost diagrammatic in the method of presenting the pathologic lesion illustrated. In the last section of the volume is a convenient ophthalmologic formulary.

The text deals with glaucoma, cataract and conditions of the ocular muscles, as well as of conditions limited in a strict sense to the external diseases of the eye. Operative treatment and technique occupy a prominent part of each section of the book. The experiences and the preferences of the author are presented.

The volume is one that should be particularly useful to general practitioners and students. It would also be useful to one practising where ocular complications of leprosy are seen. W. F.

LOVE AND HAPPINESS. Intimate Problems of the Modern Woman. By I. M. HOTEP, M.D. With a Prefatory Note by LOGAN CLENDENNING, M.D. Pp. 242. New York: Alfred A. Knopf, 1937. Price, $2.00.

THIS book deals with the little discussed side of the conflict between the basic instinctive drive for sexual satisfaction and the restricting forces of moral, religious and social ideals. It gives sanction and solace to the satisfying of these instincts, stating frankly the dangers encountered, the price paid, and the difficulties encountered in this procedure, and briefly (and glibly?) gives suggestions for coping with these factors.

The tone and temper of the book is a bit disappointing for one with the background of the author, "I. M. Hotep (?)," and the reader wonders if the frustrated female coming for help will be able easily to lay aside moral, religious and social scruples as is suggested. The crying need for revision of divorce, contraception and abortion laws to meet modern needs more adequately is forcefully stressed. This portrayal of a controversial subject, under correct supervision and guidance, can be of distinct use in handling this type of problem. L. S.

A PRACTICE OF ORTHOPEDIC SURGERY. By T. P. MCMURRAY, M.B., M.CH., F.R.C.S. (EDIN.), Director of Orthopedic Studies and Lecturer in Orthopedic Surgery, Liverpool University; Honorary Orthopedic Surgeon, David Lewis Northern Hospital, etc. Pp. 471; 178 illustrations. Baltimore: William Wood & Co., 1937. Price, $5.00.

THIS excellent volume is dedicated to Sir Robert Jones. The author has in compact and concise form given a description of the basic principles underlying the treatment of orthopedic surgery. The details of many operative procedures have been wisely omitted. No reference is made to the treatment of fractures. There are 25 chapters and a very satisfactory index. The entire text is written from the point of view that "As orthopædic surgery is concerned largely with growing and developing tissues the outlook of the surgeon should be essentially conservative." Some American orthopedists will not agree fully with this conception but to the Reviewer the case which the author makes for it is a good one. The viewpoint that medicine and surgery are interdependent is constantly kept in mind and adds greatly to the value of the work. The photographs are clear, the roentgen ray reproductions good and the diagrammatic sketches excellent.

Covering splints and apparatus, adhesions and ankylosis, the various joints and their diseases, the spine, the feet, the sequelæ of poliomyelitis, certain injuries to peripheral nerves, the affections of muscles and tendons,

rickets, and the general dyscrasias and tumors of bone in a single small volume is an accomplishment. To have done this so that it proves valuable to general practitioner, general surgeon and specialist is a real achievement.

I. R.

CONTRIBUTIONS TO MEDICAL RESEARCH. Anniversary Volume. Scientific Contributions in Honor of Joseph Hersey Pratt on His Sixty-fifth Birthday. (Reprinted from articles appearing in Annals of Internal Medicine.) By HIS FRIENDS. Pp. 983; illustrated. Printed by Lancaster Press, Inc., Lancaster, Pa., 1937. Price, $7.00.

THE sixty-fifth birthday of Joseph Hersey Pratt, M.D., of Boston, was recently celebrated and the event felicitously memorialized by his friends in the profession coöperating to publish this volume in his honor. It would be impossible properly to review in the, necessarily, limited space of this column the 80 interesting medical presentations by Dr. Pratt's friends and associates. In the Reviewer's opinion each essay may be read with sustained interest and pleasure.

One also finds listed the references to 120 contributions to medical literature by Dr. Pratt. The first article appeared, in 1895, while Dr. Pratt was an undergraduate medical student, and the latest was published in 1937. For a doctor to have acquired 65 birthdays is, in the natural order of things, commonplace; but to have utilized those years as wisely, kindly and altruistically as Joseph Pratt has done is exceptional and noteworthy. One frequently hears, within and outside the medical profession, the trite but, unfortunately, true statement, "there are too many doctors." Alas! one will never live to hear the statement, "there are too many kind, skilled and excellent physicians." Joseph Hersey Pratt, M.D., represents the medical profession at its best. He is learned, talented and skilled and is second to no other physician of his own, or any other city, in kindness and consideration for others. He is an inspiring teacher and, like all truly great physicians, he continues to be a life long student of medicine. May he long be spared to his patients, his profession, his friends, and to the citizens of that delightful city, Boston.

J. B.

A TEXTBOOK OF HEMATOLOGY. By WILLIAM MAGNER, M.D., D.P.H., Pathologist, St. Michael's Hospital, Toronto, Canada; Lecturer in Pathology, University of Toronto, etc. Pp. 395; 23 illustrations, 3 colored plates and 3 charts. Philadelphia: P. Blakiston's Son & Co., Inc., 1938. Price, $4.50.

IN the preface the author states his purpose: to present the subject of hematology "in a manner acceptable to practising physicians as well as to those primarily interested in the study of disease by laboratory methods." These twin purposes (which are to a disturbing degree definitely dissimilar twins) are approached with creditable modesty, accuracy and simplicity. The binding of the handy-sized volume is said to be "sturdy, cleanable, water resisting and vermin proof." The format is pleasing, the print large and clear, the index comprehensive and the bibliography well selected. The photomicrographs, as is generally true, are not of much value to the uninitiated; and the case reports incorporated in the text should perhaps have been presented in small type, if at all Your Reviewer recommends this book to junior and senior medical students, internes, and energetic practitioners who want a "conservative" review of current (1937) hematologic methods, views and findings.

T. F-H., JR.

PULMONARY TUBERCULOSIS IN PRACTICE. A Modern Conception. By R. C. WINGFIELD, B.A., M.B., B.Ch., F.R.C.P., Medical Superintendent, Brompton Hospital Sanatorium, Frimley; formerly Tuberculosis Officer, St. Thomas's Hospital. Pp. 122; 25 illustrations, and 1 insert (in color). Baltimore: William Wood & Co., 1937. Price, $2.50.

A NEED is filled by this compact volume, which is designed to enable the family physician to detect tuberculosis at a readily curable stage, and to coöperate with the tuberculosis specialist in the management of the tuberculous patient when sanatorium care is refused or completed. The introductory chapters, which summarize modern concepts of pathogenesis, emphasize that only in the end stages of disease are the classifical symptoms and signs of pulmonary tuberculosis obtained. The insidious clinical manifestations of minimal tuberculosis are described in detail, with stress on the need and indications for roentgenologic examination. The broad principles of treatment are discussed, with elaborate consideration only of details of direct concern to the practitioner. H. I.

INTRODUCTION TO OPHTHALMOLOGY. By PETER C. KRONFELD, M.D., Professor of Ophthalmology, The Peiping Union Medical College. Pp. 331; 32 text illustrations and 5 plates. Springfield, Ill.: Charles C Thomas, 1938. Price, $3.50.

THIS very interesting book is intended to supplement a textbook of ophthalmology for the undergraduate medical student. It is not intended as a textbook and could not be used as such. It contains much of interest to practising ophthalmologists and can be recommended for its original points of view. F. A.

THE BRAIN AND ITS ENVIRONMENT. By JOSEPH BARCROFT, Professor of Physiology, Cambridge University. Pp. 117; 30 illustrations. New Haven: Yale University Press, 1938. Price, $2.00.

THIS series of 3 lectures was delivered under the auspices of a foundation devoted to "application to human welfare . . . . by the building up of the truths of science and philosophy into the structure of a broadened and purified religion." Without this clue we should be puzzled to account for the title under which masquerades an interesting account of the author's recent work upon the physiology of the sheep embryo.

The first lecture presents an analysis of fetal movement; the second deals with the shifts at birth in blood-vessels, blood gases and their transport, and respiration. Up to this point, an array of new results is woven into a logical pattern with the clarity and charm of the author at his best. The last chapter sketches the familiar picture of the nervous responses to extreme shifts in tension of the blood gases in the adult human.

G. McC.

NEW BOOKS.

A Textbook of Clinical Pathology. Edited by ROY R. KRACKE, Emory University, Georgia, with the assistance of DOCTORS A. P. BRIGGS, L. W. DIGGS, GEORGE HERRMANN, F. M. JOHNS, F. B. JOHNSON, R. MCBURNEY, H. E. MELENEY, A. J. MILLER, F. P. PARKER, V. P. SYDENSTRICKER and J. G. WAHLIN. Pp. 567; 205 illustrations and 31 plates (19 in color). Baltimore: William Wood & Co., 1938. Price, $6.00.

The Anemias. With Special Reference to Pernicious Anemia and the Use of Liver Extracts and Supplementary Factors in the Treatment of Anemias. Supplement. Blood Morphology in Diagnosis. A Series of Six Articles Reprinted from The Physician's Bulletin. Pp. 98; 7 colored plates. Indianapolis: Eli Lilly and Company, 1938.

Leukemia and Allied Disorders. By CLAUDE E. FORKNER, A.M., M.D., Assistant Professor of Clinical Medicine, Cornell University Medical School, and Assistant Attending Physician, New York Hospital, etc. Pp. 333; 73 illustrations and 6 colored plates. New York: The Macmillan Company, 1938. Price, $5.00.

Athletic Injuries. Prevention, Diagnosis and Treatment. By AUGUSTUS THORNDIKE, JR., M.D., Surgeon in the Department of Hygiene, Harvard University; Assistant in Surgery, Harvard Medical School, etc. Pp. 208; 104 illustrations. Philadelphia: Lea & Febiger, 1938. Price, $3.00.

League of Nations. Bulletins of the Health Organisation. Vol. VI, No. 5 (October, 1937) and No. 6 (December, 1937). Pp. 211 (No. 5), 258 (No. 6). New York: Columbia University Press, 1938. Price, 65c each.

Pediatric Surgery. By EDWARD C. BRENNER, A.B., M.D., F.A.C.S., Director of Surgery, Riker's Island and Detention Hospitals; Attending Surgeon, Midtown Hospital, etc. Pp. 843; 293 illustrations. Philadelphia: Lea & Febiger, 1938. Price, $10.00.

The Biological Standardisation of the Vitamin. By KATHARINE H. COWARD, D.Sc., Reader in Biochemistry, University of London; Head of the Nutrition Department, Pharmaceutical Society of Great Britain. Pp. 227; 44 figures and 29 tables. Baltimore: William Wood & Co., 1938. Price, $4.50.

Thoracic Surgery. A revised and abridged edition of Sauerbruch's Die Chirurgie der Brustorgane. By FERDINAND SAUERBRUCH, Professor of Surgery in the University of Berlin, and LAURENCE O'SHAUGHNESSY, F.R.C.S., Hunterian Professor in the Royal College of Surgeons of England; Consulting and Thoracic Surgeon to the British Legion Sanatorium, Preston Hall, and to the Nottinghamshire County Council, etc. Pp. 394; 215 illustrations and 15 colored plates. Baltimore: William Wood & Co., 1937. Price, $13.50.

Christianity and Sex. By RICHARD C. CABOT, M.D. Pp. 78. New York: The Macmillan Company, 1938. Price, $1.00.

Essentials of Obstetrical and Gynecological Pathology with Clinical Correlation. By MARION DOUGLASS, M.D., F.A.C.S., Assistant Professor of Gynecology, Western Reserve University; and ROBERT L. FAULKNER, M.D., Senior Clinical Instructor in Gynecology, Western Reserve University. Pp. 187; 148 illustrations. St. Louis: The C. V. Mosby Company, 1938. Price, $4.75.

Internships and Residencies in New York City, 1934–1937. Their Place in Medical Education. Report by The New York Committee on the Study of Hospital Internships and Residencies. JEAN ALONZO CURRAN, M.D., Executive Secretary. Pp. 492. New York: The Commonwealth Fund, 1938. Price, $2.50.

This study, sponsored in 1934 by the Commonwealth Fund, has been carried on by a large committee of New York physicians. The report deals with such topics as "Resources for Intern and Graduate Education in New York City;" "The History of Internships and Residencies;" "The Relation of Intern and Graduate Education to Practice: A Survey of 1904 Practicing Physicians, Graduates of New York City Medical Colleges;" "Geographic Distribution of the Medical Colleges Supplying House Staffs to New York City Hospitals;" "Factors Contributing to House Staff Efficiency;" "Hospital Libraries and Their Use;" "Preparation and Training of the Intern;" "Organization of the Internship Program and Capacity of the Hospital in Relation to Quality of the Internship;" "Residencies and Fellowships in New York City Hospitals." There are 160 pages of appendices, including an 18-page bibliography.

Les Épidémies et Les Perturbations Électromagnétiques du Milieu Extérieur. By Prof. Dr. A.-L. Tchijevsky. Pp. 239; 120 illustrations. Paris: Editions Hippocrate, 1938. Price, 40 fr.

Some Account of the Pennsylvania Hospital From Its First Rise to the Beginning of the Year 1938. By Francis R. Packard, M.D. Pp. 133; illustrated. Philadelphia: Printed by the Engle Press for the Pennsylvania Hospital, 1938. Price, $2.50. (Books are obtainable from the Pennsylvania Hospital, 8th and Spruce Streets, Philadelphia, Pa.)

Advances in the Therapeutics of Antimony. By Prof. Dr. Phil. Nat. Hans Schmidt and Dr.-med. F. M. Peter. With a Preface by Dr. Philip Manson-Bahr, C.M.G., D.S.O., M.D., F.R.C.P. Pp. 257; 10 illustrations. Leipzig: Georg Thieme, 1938. Price, Paper, M. 18; Bound, M. 19.50.

Papworth. The Sims-Woodhead Memorial Laboratory. Research Bulletin for 1937. Vol. 1, No. 2. Illustrated. Papworth: Pendragon Press, 1938.

Human Powers and Their Relations. By K. W. Monsarrat. Pp. 289; 60 figures. London: Hodder & Stoughton, Ltd., 1938. Price, 10/6.

NEW EDITIONS.

Klinik und Therapie der Herzkrankheiten und der Gefässerkrankungen, Vorträge für Praktische Aerzte. By Privatdozent Dr. D. Scherf, in Wien. Pp. 319; 10 illustrations. Fourth edition. Wien: Julius Springer, 1938. Price, Paper, Rm. 7.20; Bound, Rm. 8.40.

A Diabetic Primer for Children. By Alfred E. Fischer, M.D., Adjunct Pediatrician and Chief of the Children's Diabetic Clinic, Mount Sinai Hospital, New York City, etc. Pp. 53 (lithoprinted). Second edition. Privately published. Copies may be obtained from Dr. Alfred E. Fischer, 73 East 90th St., New York City.

Pharmaceutical Latin. For Pharmaceutical, Medical, Dental and Veterinary Students and Practitioners. By Jacob S. Dorfman, Assistant Professor of Pharmacy, Columbus University College of Pharmacy, etc. Pp. 146. Second edition, thoroughly revised. Philadelphia: Lea & Febiger, 1938. Price, $2.00.

Tuberculosis Among Children and Young Adults. By J. Arthur Myers, Ph.D., M.D., F.A.C.P., Chief of Medical Staff and Director of Tuberculosis Activities, Lymanhurst Health Center; Professor of Preventive Medicine, University of Minnesota. With Chapters by C. A. Stewart, M.D., Ph.D., Clinical Professor of Pediatrics, University of Minnesota; Paul W. Giessler, M.D., F.A.C.S., Assistant Professor of Orthopedic Surgery, University of Minnesota. An Introduction by Allen K. Krause, M.D., Lecturer in Medicine, Johns Hopkins University. Pp. 401; 71 illustrations. Second edition. Springfield, Ill.: Charles C Thomas, 1938. Price, $4.50.

Progressive Relaxation. A Physiological and Clinical Investigation of Muscular States and Their Significance in Psychology and Medical Practice. By Edmund Jacobson, A.M., Ph.D., M.D., Laboratory for Clinical Physiology, Chicago. Pp. 494; 89 illustrations and 10 tables. Revised edition. Chicago: The University of Chicago Press, 1938. Price, $5.00.

Die Chirurgie des Kropfes. By Hofrat Dr. Karl Urban, Vorstand der chirurgischen Abteilung und Leiter des Krankenhauses der Barmherzigen Schwestern in Linz a. D. Pp. 112; 51 illustrations. Second edition, enlarged. Wien: Franz Deuticke, 1938. Price, Paper, M. 7; Bound, M. 9.

PROGRESS
OF
MEDICAL SCIENCE

MEDICINE

UNDER THE CHARGE OF
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PELLAGRA.

In the 200 years since pellagra was first recorded in medical literature, few diseases have equalled it in the elusiveness of its etiology, the scope of its clinical aspects and the disappointments in its treatment. Casel recorded the disease in the Asturias in 1735. Pujati, of Venice, described it about 1755, but its recognition by Italian physicians was known as far back as 1720.[71] Frapolli named the disease pellagra in 1771. Estimates show that by 1830, about 5% of the population of northern Italy had pellagra. The diagnosis of the disease in France, the Balkans, Egypt and, in 1863, in the United States, established many widespread endemic areas and led eventually to the recognition of its world-wide distribution. Endemic centers have also been found in India, Japan, Australia, South America and Mexico. Sporadic cases have been reported in practically all lands.

Etiology. The exact cause of pellagra is unknown. The disease was early associated with the food habits of its victims, a contention which, although changed entirely in its interpretation, is the main thesis of most investigators today. Ideas of etiology have been colored naturally both by the experiences of the investigators putting them forth, and by the general concepts of disease in the corresponding era. Indeed, the evolution of medical thought in the past 200 years may be seen in the changing views on the etiology of pellagra.

Maize. Early association of pellagra with the ingestion of maize directed attention to this substance as the causative agent. In 1789, "spoiled" corn was accused, and even today an association of pellagra with the ingestion of corn is held by some, despite the fact that the disease occurs in groups never having eaten maize. Also, in many races using maize as a staple diet, pellagra is conspicuously absent.[70d] The latter fact does not fit well with recent suggestions that the low value of protein in maize as compared to that of wheat may lead to pellagra through an inadequate supply of essential proteins.[85] Stockman and Johnson[73] found that a maize diet caused death in monkeys as a result of central nervous system changes like those of pellagra. An

acid was found in maize which, when administered by stomach or hypodermically, produced the same results. Other cereals, such as rice, rye, wheat and oats, produced similar results even when the diet was rich in vitamin-containing foods. In rabbits, skin lesions and thinning of bones occurred. Still, Spies and DeWolf[66] showed that 10 pellagrins taking large quantities of corn whiskey with an adequate diet and yeast showed no toxic symptoms, indicating again a probable deficiency.

Infection. The bacterial era naturally led to the search for an infectious agent as the cause, and later the recognition of deficiency diseases to a nutritional etiology. Evidence for the infectious theory is entirely indirect and far from convincing. Such points as the seasonal character of the disease, with occurrence chiefly in the late spring and summer, symptomatic improvement with the sudden onset of cool weather and alleged cure by the use of arsenic, simulate the events in certain infectious diseases, but prove nothing. The association of the occurrence of the disease with unsanitary conditions, as pointed out by the Thompson-MacFadden Commission,[58] and the decrease in incidence of pellagra with improvements in sanitation are suggestive, but again prove nothing. The same may be said of the occasional occurrence of the disease in well-to-do families on liberal diets. Although many infectious agents, especially in relationship to infestation of the gastro-intestinal tract, have been postulated, no organism has been assignable as the cause. Inability to demonstrate an organism has led to the filtrable virus theory[78] with the skin eruption and mucous membrane lesions attributed to secondary involvement of the nervous system. Goldberger[26] was unable to transmit the disease from man to man. Blood intramuscularly or subcutaneously, nasal secretions by application to the mucosa of the nose and mouth, and dermal scales, urine and feces of pellagrins by mouth, administered to normal subjects, did not lead to the development of pellagra. Similar experiments in monkeys were unsuccessful.[44] Epidemiologic studies appear to be the only support of the infectious theory and Eddy and Dalldorf[17] remind us that such evidence of the infectious nature of scurvy was collected and is now forgotten. One cannot accept the infectious theory until new and conclusive evidence is adduced for its support. That certain infections may play a contributory rôle to the development of pellagra will be discussed below.

Nutrition. The nutritional theory holds the center of the stage today. The lack of definite evidence for the infectious theory contrasts with the wealth of pointed and controlled investigations favoring the nutritional hypothesis. One of Goldberger's experiments has already been cited. Although he and others up to the present time have not isolated a pure chemical substance or vitamin which has been shown to be the agent missing from the diet of pellagrins, prevention and remission by the use of proper diet and the production of the disease in healthy subjects by directed limitation of their diets stand as important evidences of a deficiency as the cause. In the Army, where an adequate dietary is maintained, pellagra is very rare,[25] even in countries where pellagra is highly endemic. Prior to the World War, pellagra was practically unknown in the Italian, Egyptian and American armies. Although pellagra is endemic among the civilians in the area surround-

ing Fort Benning, Georgia, there has been only 1 case among the soldiers since its establishment.

The work of Goldberger and his co-workers[26,29–31] is too well known to require detailed review here. In a period of 3 years he observed 414 pellagrins in 4 institutions. No changes were made in the conditions of living except the addition to the diet of meat, legumes and milk. Only 1 recurrence was noted under these conditions, whereas a return to the old type diet in 1 of the institutions was followed by an incidence of about 40%, with disappearance again on resumption of the improved diet.

The production of pellagra in man by dietary control proved to be a crucial and important bit of evidence favoring the deficiency theory. Of 11 normal convicts (volunteers) placed on a pellagra-producing diet, 6 showed, in 5 months, evidence of typical dermatitis and nervous and gastro-intestinal symptoms.[29] Later, Walker and Wheeler[81] repeated the same experiment, with positive results, in 17 of 18 epileptic subjects, who developed stomatitis, diarrhea and bilateral symmetrical skin lesions in approximately 6 months. A control group on the same diet plus greens showed no pellagra in 1 year.

The application of similar procedures to the dog as a test animal disclosed the development of the disease known as black tongue. The same picture has been easily reproduced by others.[61] This disease is, therefore, regarded as the counterpart of human pellagra, especially since Denton[16b] demonstrated that the lesions in the dog were very similar to those found in the intestinal tract of patients with pellagra. Fusospirochetal organisms present in the mouth are said to precipitate the oral lesions and act as a reliable indicator of the nutritional status.[61] Blankenhorn and Spies,[9] in showing the frequency of glossitis and stomatitis in alcoholism in the human, found in the swollen, deeply reddened, tender gums many fusospirochetal organisms, again suggesting a relationship to black tongue.

Dogs with experimental black tongue have been used as test animals in the evaluation of foods for their pellagra-preventive properties. Such foods as turnips, sweet potatoes, onions, carrots, milk, certain fish, lean meat, and a variety of greens, wheat germ, and especially yeast, have been shown to be valuable as pellagra-preventive agents. With the use of these and similar foods, Goldberger and Tanner[28] were able to demonstrate that proper diet was both preventive and curative for pellagra. As yet, no one has successfully shown that the pellagra-preventive and antiblack tongue properties of food can be separated to indicate the presence and close association of two separate factors.

Careful investigation into the economic conditions in areas in which pellagra is endemic has demonstrated satisfactorily that the endemic nature of the disease is not necessarily an indication of infectious origin.[56b] The disease occurs chiefly in rural districts. For example, in 1932, 500 cases were reported in Virginia, and 45% of these were in 6 counties. Likewise, in the first 8 months of 1933, 48% of 717 cases in North Carolina occurred in 7 counties. A similar irregular distribution was found elsewhere. Common to these areas was the factor of a restricted food supply and the cultivation of non-food crops, such as tobacco and cotton, or devotion to rural industry, such as

mining and cotton mills. Rural sections devoted to the raising of livestock or food crops had no major pellagra problems. The seasonal incidence—40% of the cases in June in some areas—was related to the reduced consumption of fruit, fresh vegetables and milk, and regression of the disease to their increased consumption. Similarly, it has been shown that depression in the cotton market has led to an increase of pellagra in cotton-producing areas until these farmers were forced, through a lack of demand for cotton, to plant and raise a variety of food at home.

Protein Deficiency. The inability of investigators to isolate a single substance which could be regarded as the deficient agent in pellagra has led to the supposition that this disease may not be a single avitaminosis, with a pellagra-preventive vitamin, but raised the possibility of a deficiency of protein of "high biological value."[86] The latter may be either a single amino-acid deficiency, or a toxic substance, derived for example from a maize diet, which requires for its correction, or "neutralization," sufficient "good" protein.[12] Such theories as these have usually been attempts to fit modern concepts into old theories, such as the maize theory. Here, toxic corn products in the whiskey, producing alcoholic pellagra, are supposedly neutralized by "good" protein. Against the protein deficiency theory is evidence that protein in a purified form[35] exerts little, if any, protection in animals with black tongue, and yeast extracts, which are practically nitrogen-free,[34] will prevent and cure pellagra in patients on an otherwise pellagra-producing diet.

Vitamin B Complex. Since pellagra-preventive (P–P) properties remain following destruction of the heat-labile vitamin B_1, the heat-stable fraction is known to contain the essential factor, or factors. Attempts to isolate this factor by animal experimentation have led to a mass of confusing data. In 1926,[27] it was shown that rats on diets low in B_2, but adequate in B_1, developed dermatitis and stomatitis. These observations led the way to numerous demonstrations of a multiplicity of antidermatitic factors in the B_2 complex, with variable results depending on the species used as test animals. The isolation of the flavins suggested their possible identity as the P–P factor. György showed that vitamin B_1 and flavins did not prevent the development of dermatitis in rats, but that another substance obtained from yeast did. This he termed B_6 and thought it the same as the "Y" factor of Chick and Copping.[13] Birch, György and Harris[7] showed that at least 3 factors were present in so-called "B_2." These were lactoflavin, B_6, and the P–P factor, the last of which was apparently identical with the antiblack tongue factor. Further reports have shown that flavin is ineffective in the prevention and cure of black tongue.[43,57] A fourth factor, the filtrate or chick pellagra factor, was found to differ from the P–P factor by differences in distribution in foods.[40] Jukes[39] later showed further discrepancies in the distribution of these two factors. Pellagra has been successfully treated with preparations containing the filtrate factor,[23] but such preparations have not excluded other possible pellagra-preventive substances. Lactoflavin and B_6 have not been satisfactorily related to human pellagra,[15a,23] and both have been shown, in their distribution, to fail to correlate with the pellagra-preventive properties of foodstuffs.[7]

The latest bidder for identification as the P–P factor is nicotinic acid. It is not identical with either flavin, vitamin B_6, or the chick dermatitis factor.[15b] Although demonstrated by Funk in vitamin B preparations 25 years ago, present interest in this preparation has been stimulated by the demonstration of Elvehjem and his associates,[19] in 1937, that nicotinic acid is active in the cure of canine black tongue, and that it is present in liver, from which they isolate it. Harris[36] has shown, in monkeys having the analogue of experimental human pellagra on a pellagra-producing diet containing the other known constituents of the B_2 complex, a curative effect with nicotinic acid; but warns that further work is necessary to see if nicotinic acid was the sole deficiency in such a diet. The compound is effective in the treatment of the stomatitis and dermatitis of endemic pellagra, as will be discussed later. Its place in the etiology of the pellagra is not yet settled. The evidence, given in the section on Treatment below, strongly favors the assumption that it is the P–P factor of Goldberger, a precursor of it, or one factor of a multiple deficiency state. Harris[36] suggests that it may be the less active form of a more active variation formed from it within the animal body.

The frequent occurrence of pellagra in the face of an adequate diet in patients with derangements of the gastro-intestinal tract, such as amebic dysentery, rectal stricture, and carcinoma of the stomach, has led to the use of the term "secondary pellagra." In such patients the gastro-intestinal disease has been assumed to interfere with the absorption or production of the P–P principle or principles. If such disease is etiologically important in the development of pellagra in these patients, the term "conditioned deficiency" may be extended to include such patients.

Multiple Deficiencies. "Why apparently identical conditions should sometimes produce pellagra, sometimes hyperchromic megalocytic anæmia, sometimes simple microcytic anæmia, sometimes polyneuritis presumably from deficiency of vitamin B_1, and most often nothing abnormal, is a complex problem that awaits solution."[59] Such inconsistencies as these and the clinical findings, together with the inadequacies of the present theories of pellagra to explain the occurrence of the disease have led Sydenstricker and his associates[76] to suggest that pellagra is a conditioned deficiency of the same order as pernicious anemia, that an intrinsic factor (from the stomach) must act with an extrinsic factor in a manner similar to the action of Castle's factors for pernicious anemia to produce an essential substance necessary for the prevention of pellagra. Others have also suggested this theory.[49,70d] By variations in the amount of this hypothetical intrinsic factor, and the organism's ability or inability to regenerate it in the presence of adequate supplies of extrinsic factor, the response of pellagrins to therapy is explained. A prolonged deficient intake of extrinsic factor might lead to exhaustion or failure of production of intrinsic factor with the development of pellagra. In some a sufficient supply of intrinsic factor might remain or regenerate to make use of the extrinsic factor. Imitation of Castle's experiments on pernicious anemia with patients on pellagra-producing diets[76] supported the hypothesis. Some patients supposedly retain enough intrinsic factor to recover on diets deficient in B_2; others are able to regenerate the intrinsic factor rapidly

in the presence of an adequate supply of extrinsic factor and recover on high-protein feeding. Others, with the intrinsic factor totally lacking and unable to regenerate it with dietary feeding, may recover under substitution therapy, or die before such therapy is instituted. Stannus[70d] has speculated on the rôle of corn, alcohol, carcinoma, and other factors in interference with production of intrinsic factor. More work and less postulation is now necessary to establish or disprove these concepts.

The idea that pellagra may be a multiple deficiency is not new.[32,82] The numerous reports of diseases associated with stomatitis and glossitis[70c] also suggest this possibility. Spies and Aring,[65] in studying the peripheral neuritis associated with pellagra, could not distinguish it from the peripheral neuritis of beriberi. They found that vitamin B_1 containing foods and intravenous injections of the crystalline vitamin gave prompt relief of the neuritic pain, but did not cure the glossitis and stomatitis. Nicotinic acid in 3 cases completely healed the severe stomatitis and glossitis, but did not cure the peripheral neuritis. Although all patients with pellagra do not have neuritis, these results strongly favor the multiple deficiency theory. Until a substance is isolated which will cure, by itself, the triad diagnostic of pellagra, it will not be known whether pellagra is a single disease caused by one or any deficiency, a syndrome caused by more than one deficiency, or an expression of multiple deficiencies necessarily acting together.

Photosensitization. The skin lesions, and particularly their relationship to exposure to sunlight, have led to photodynamic hypotheses. Certain diseases of animals, such as *geeldikkip*,[51] a poisoning caused by the excessive feeding of Tibulus to small stock in Africa, are known to occur from the ingestion of porphyrins, which photosensitize the skin. Ingestion of hematoporphyrin by man in adequate dosage is known to produce lesions in the skin on exposure to sunlight. These effects have been reviewed recently in these columns.[5] Observations on pellagrins by Bassi[3] in Italy, in 1934, and later by Ellinger and Dojmi[18] and Beckh, Ellinger and Spies[4] have shown elevated values for porphyrins in the urine of pellagrins in the acute stages of the disease. Whether photosensitization of the skin by porphyrins is important in the production of the pellagraderm is unknown, and their source, although probably from red blood cell destruction, is obscure. Scott, Turner and Mayerson[55] were unable to detect spectroscopically the presence of hematoporphyrin in the serum of pellagrins.

Selenium is another substance which is sensitive to light and occurs in the body in minute amounts.[1] Animals eating plants containing selenium obtained from the soil may die on exposure to sunlight. The symptoms produced are gastro-intestinal, nervous and dermal.

Selenium is related to sulphur and some plants cannot distinguish metabolically between the two. Sulphur metabolism is deranged in pellagra, as Payne and Perlzweig[48] have reaffirmed. The increased urinary excretion of sulphates and the reduction of sulphur in the central nervous system in pellagra prompted these observers to study the sulphur content of the fingernails. In 14 cases with extensive dermatitis, the cystine content was markedly reduced while the total protein content remained unchanged. With improvement, and in partially or completely cured cases as well as in those without dermatitis, there were no marked changes.

Studies are under way to determine the distribution of selenium in the soils.[42] Results of such investigations indicate that selenium is present in the soils of some districts in sufficient quantities to make it an agricultural problem. Thus far, these areas with seleniferous soils are chiefly western grazing lands and do not correspond to the areas of endemic pellagra. A relationship to pellagra, therefore, seems unlikely.

This section on etiology of pellagra may rightly end with repetition of its first statement. The exact cause of pellagra is unknown. The views on etiology are so divergent, and the approaches to the problem so different, that in the future, when the etiology is definitely known, many present concepts will seem amusing.

Pathologic Anatomy. Well-controlled observations on the pathologic changes in pellagra are few. Those of Denton[16a] are particularly significant because of the exclusion of bodies with lesions of other unknown diseases and because autopsies were done within a few minutes after death. He found in general that the nutrition was in proportion to the duration of the disease. Gross lesions of the stomach were found in only 1 case, a pseudomembranous inflammation of the cardia. The anatomic picture at autopsy was sufficiently definite to warrant a diagnosis without clinical history. The mucous membranes of the mouth and esophagus showed a brownish-red color with and without small necrotic lesions. A dark red color of the small intestine and an intense colitis were characteristic. Such changes, together with the skin lesions, left no difficulty in postmortem diagnosis.

Skin lesions were found before erythema had appeared. The duration of these lesions, Denton believes, must, from the histologic point of view, be dated from the first subjective symptoms, such as a feeling of stiffness and tenseness before the lesions were visible. He found first a stage of injury, or fibrolytic stage, then a reactive or dermatitic stage, followed by repair, compensatory vascular ectasis or erythematous stage, and finally the cicatricial or atrophic stage. The presence of findings before the visibility of the lesion is extremely important, for, as will be stated in the sections on *Symptomatology* and *Diagnosis*, recognition of the disease before the skin eruption can be seen, pellagra *sine eruptione*, is of extreme clinical importance.

Certain of Denton's findings in the skin bear upon the etiology of the disease. There was no evidence of the skin lesions being infectious in nature. The sequence and character of the cutaneous changes were consistent with their being photodynamic effects, with a slight resemblance to some of the lesions of Roentgen ray dermatitis. However, he found that the reaction of the tongue, pharynx, and esophagus was essentially the same with stages of injury, reaction, compensatory vascular ectasis and atrophy, and that these lesions were the most contant and consistent in the disease. Yet these changes were so situated that some other factor than radiant energy must be responsible for them, and most likely for the skin lesions as well.

As far back as 1789, it was recognized that the skin lesions could not be explained by solar irradiation alone. Lesions are precipitated by irradiation, it is true, and reports are on record of the absence of lesions from the common sites when these areas are protected, as, for example, in the veiled women of Turkey. Spies[64f] calls attention to the fact that lesions are most common in the spring and the sun's rays are most

powerful in the summer. The necessity of avitaminosis for the development of lesions would make this relationship lose importance. Still the lesions may affect any unexposed area, appear in patients confined to bed, and exposure of the entire body to sunlight may result in lesions only in the usual areas. Further discussion of the effects of sunlight in the following sections will show that a variety of trauma, such as pressure and chemical irritants, have precipitated skin lesions, and that sunlight is probably only a convenient one of many traumata capable of precipitating them.

The occurrence of Vincent's organisms in the mouth with glossitis and stomatitis has already been mentioned. Such infection occurs in pellagra as well as in black tongue. In the colon Denton found no pathognomonic changes but aggregate changes were quite characteristic. Numerous cysts formed in the crypts of Lieberkuhn, a change said to occur only in pellagra and sprue, but very infrequently in the latter.[87] Dilatation of the submucosal vessels and cellular infiltrations were also seen.

Lesions of the central nervous system have been interpreted both as by-products[16a] of and as primary changes [78] in the disease. Such findings are not necessarily proportional to the acuteness and severity of the disease. The lesions themselves are non-specific, with changes in the postero-lateral and postero-median columns of the cord and in the spinal sympathetic and posterior ganglia. In the spinal cord, degeneration of the medullary sheaths in both the posterior columns and in the crossed and uncrossed pyramidal tracts may ultimately lead to gliosis. Such lesions are considered characteristic of, but do not occur exclusively in, pellagra.[90] They have been produced in dogs on deficient diets.[89]

Clinical Aspects. I shall consider only the new and less well-known aspects of pellagra. The familiar three D's—dermatitis, dementia and diarrhea—make a trinity too well known to deserve comment. The fourth—death—is heralded by inadequate treatment. Stannus[70b] says of the three D's, "while we may admire the alliterative ability of the author of this diagnostic slogan, it is probably true, if it be said, that nothing has done more to stifle the recognition of early cases and those that do not manifest what have been called the classical symptoms." In the light of the findings already mentioned, that demonstrable skin changes occur before the eruption is clinically manifest, one can well understand statements that many and possibly the majority of cases in an endemic area do not present classical symptoms and may go unrecognized. Physicians must awaken to the remarks of Stannus that pellagra is a disease presenting great variety in its picture, course and symptomatology as well as in intensity of individual symptoms. One wonders how often pellagra is masked under such diagnoses as dyspepsia, neurasthenia and colitis. Gradual deterioration of health, a tendency to hypochrondriasis, mild attacks of mental depression, failure of mental and bodily vigor, periodic digestive disturbances with abdominal discomfort, constipation with attacks of diarrhea, a sore mouth or tongue, soreness at the angles of the mouth, vertigo and indefinite pains are but a few of the symptoms which may precede, at times by years, a frank attack of pellagra.[70b]

To those physicians not seeing pellagra frequently, and especially

to those outside endemic centers, the wide variations in the course of the disease are little known. The courses of acute and chronic pellagra may be as different as those of acute and chronic leukemia, one with an acute fulminating course leading to early death, the other with exacerbations and remissions leading, with proper treatment, and here unlike leukemia, to cure.

Pellagra occurs at all ages. Statements vary particularly in respect to occurrence in children. Some[84] consider the disease rare in childhood, but others[72] commonly find it below the ages of 12 to 15, and it has been reported under the age of 1 in breast-fed infants of pellagrous mothers. The dermatitis is said to be mild in children; and in infants, sore mouth, diarrhea, and restlessness commonly appear before the dermatitis. Some believe acrodynia to be an infantile form of pellagra.

Since 1913, Stannus has stressed as an objective sign a peculiar soreness at the angles of the mouth. This he terms "angular stomatitis," which, together with marginal glossitis, is among the earliest signs, a "prepellagrous" finding, so to speak. At this early stage similar lesions have been noted on the vulva, vagina, margin of the anus and perineum, and on the free margin of the prepuce. In the full-blown disease, lesions may appear also about the internal and external canthi and on the nostrils as well. Scrotal lesions occurred in 19 of 131 pellagrins in one series, 4 of whom had no other pellagrous exanthem. Many observers have noted this sign. The nail-bed is an often forgotten site of involvement.[70b] Pigmentation and deformity of the nails of the fingers and toes may result. Desquamation in the interdigital clefts may occur[6] and persist after other manifestations have disappeared.

Statements that the severity of the skin lesions does not parallel other symptoms have been proved many times. The author has often seen regressing skin lesions in the presence of ever increasing mental symptoms, terminating in death. Spies[64a,b,d,f] has seen skin lesions regress in patients on pellagra-producing diets, while the stomatitis was increasing. He also showed that exposure of lesions to sunlight and ultraviolet radiation did not prevent healing in patients on a pellagra-producing diet.

The lack of correlation between the occurrence of skin lesions and solar irradiation in some patients has already been mentioned. Some further facts on this relationship have been uncovered by Smith and Ruffin.[60] They reviewed previous attempts to produce lesions by exposure and successfully brought out such lesions in 13 of 35 patients. After treatment with the P–P factor only 1 developed lesions on re-exposure, indicating the importance of the test in determining activity. Fouts and Zerfas[24] were able to elicit eruptions in the same manner. The appearance of skin lesions with no definite relationship to solar irradiation has caused much confusion in the interpretation of the genesis of the lesions. Bass[2a] has noted lesions at points of pressure, such as over the buttocks and elbows in patients confined to bed, on the heels, groins and shoulders, over prominent veins and in areas in which skin surfaces are approximated. Irritation of the skin by heat, Roentgen radiation, or chemicals may affect the distribution of the lesions.[21] Such evidence as this suggests that trauma plays an important rôle in

the precipitation of lesions and that sunlight is but a convenient and common one of many such traumata.

Skin eruptions other than the usual pellagraderm are not uncommon. Most interesting is the seborrheic dermatitis to which Bass[25] and others have called attention. It is found most characteristically upon the nose, cheeks, forehead, and chin just below the mouth, but occurs at times elsewhere. A folliculitis[70b] has been described in pellagra, the kerato-follicular lesions of Majocchi. Various observers[77,87] have noted these lesions, especially on the extensor surfaces of the arms and on the thighs, the buttocks and the torso. Clinically they fit the description of those found in avitaminosis A.[88] Sabry[54b] has attempted to show that pemphigus is a form of pellagra, occurring in areas where pellagra, as such, is unknown. These conclusions are reached upon the hypothesis of defective oxidation of "dopa" in the skin.

Evidence of involvement of the heart in pellagrins has been brought out by Feil.[20] Of 38 patients with moderate to severe pellagra he found electrocardiographic abnormalities in 19 (50%), 14 of whom had no complication which might alter the electrocardiogram. He concluded that the heart is affected by pellagra. However, Porter and Higginbotham[50] found no characteristic electrocardiographic changes and explained those found by vascular or toxic complications. In 48 endemic pellagrins, they found no evidence of congestive heart failure.

Mental symptoms have been reported in as few as 4 to 15% of patients.[38] Again, the usual symptoms and signs will not be reviewed here. Pellagra may actually cause the mental disturbance, may act as a precipitating factor for other well-recognized types of nervous disease, or may, itself, result from mental disease which interferes with the proper intake of food. Nervous symptoms caused by pellagra may appear early in the disease, especially headache, vertigo, weakness, insomnia, burning sensations of the feet and other parts of the body, and depressive periods. Later inequality of the pupils, numbness, paralysis of the sphincters, ataxia and Romberg's sign may occur. Motor involvement may be due to peripheral neuritis. Hemiplegia and paraplegia have been described with restoration of function following adequate treatment.[8]

Certain laboratory data are of interest. Achlorhydria has been confirmed as a common finding.[6,47] In 107 typical endemic cases, 77 (72%) showed absence of free hydrochloric acid and the use of histamine did not change the percentage. There was no implication in this study that achlorhydria was a primary or uniformly antecedent manifestation of pellagra. In some instances following treatment normal function returned.

Both macrocytic and microcytic anemia have been found. Bone-marrow studies[41] have shown megaloblastic and pro-erythroblastic characteristics but not to the same degree as in sprue or pernicious anemia. Less than half of Turner's patients[79g] had anemia, all of the microcytic variety and varying from mild to very severe.

The association of deranged gastric function and anemia in pellagra with some resemblances to pernicious anemia, has led to many comparisons of these diseases. That pellagra is essentially different is shown by the demonstration that the gastric secretions of pellagrins contain the "intrinsic factor" of Castle. This factor should not be

confused with that postulated by Sydenstricker. It has also been shown that the chemical substance or substances in yeast effective in the treatment of pellagra is probably not the "extrinsic factor" of Castle[69] nor is nicotinic acid.[68]

Turner[79b,c] has found a tendency toward low serum albumin concentration, developing after the pellagra is manifest and remaining long after diagnostic evidence of the disease has disappeared in spite of adequate diet. He interpreted this finding as possibly the result of disturbed digestion and absorption of proteins from injury to the digestive system. Such determinations may be of value in estimating the severity of the pellagra and in furnishing one criterion of cure. Evidence of disturbed serum calcium and serum electrolyte concentration[79d,e] and changes in the circulating blood volume[79f] were also found.

Reference has already been made to "secondary" pellagra in relationship to defective absorption of essential dietary factors or defective production of an intrinsic factor. Regardless of the ultimate explanation of secondary pellagra, its occurrence in the presence of a wide variety of diseases of the gastro-intestinal tract, diseases usually entirely unconnected with pellagra, is quite common.[59,79a] These lesions vary from esophageal and gastric defects, such as carcinoma, chronic gastritis, gastric ulcer with operative shunts, to ulcerative and tuberculous colitis, rectal stricture (lymphogranuloma inguinale), amebiasis, bacillary dysentery, carcinoma of the large intestine, rectovaginal fistula, and others. The frequency of pellagra in such conditions, with adequate dietary intake, emphasizes the importance of suspecting the presence of some latent defect in pellagrins with such a dietary history.

Diagnosis. The diagnosis of pellagra is purely clinical. Whether it identifies a single disease caused by a single etiologic factor or a syndrome due to more than one cause is unknown. The diagnosis may be one of the simplest or one of the most difficult in medicine. The presence of the trinity—pellagraderm, nervous and gastro-intestinal symptoms—makes diagnosis unmistakable. However, the triad is not always present. For example, Turner[79b] found glossitis in 26 (61.9%) of 42 patients. Mental symptoms are said to occur in approximately one-third to one-fourth of the patients.

When the characteristic skin eruption is absent, certainty in diagnosis becomes most difficult. The remarks already made under Pathology and Clinical Aspects indicate this. In endemic areas where the diagnosis of pellagra *sine eruptione* may be expected with a fair degree of accuracy, approximately 60 to 70% of the patients[70b] present the exanthem. Such groups do not, however, include patients not sufficiently ill to seek medical aid, nor those with entirely non-specific symptoms. The sore tongue, burning sensations in the feet, diarrhea, and mental symptoms may or may not, by themselves, be sufficient to suggest the diagnosis, and their recognition and possible significance depend to a great extent upon the clinical training and awareness of the diagnosis on the part of the examining physician. A perusal of the report of Stannus[70a,c] on pellagra-like conditions will show the interested reader how frequently disease with the essential findings of pellagra, dermatitis excepted, is reported without reference to the possibility of pellagra, even in the presence of obvious food deficiency.

Diagnosis in certain diseases of known etiology when latent, sub-

clinical or with non-specific symptoms, is simplified by the isolation of the causative organism or by specific test. But in such diseases as rheumatic fever or pellagra, where no such aid exists, when typical clinical findings are absent and clinical awareness suggests the diagnosis, the seriousness of the disease is sufficient to justify error on the side of treatment for that disease. There is no doubt that a specific test for pellagra would often surprise the examiner by revealing the presence of the disease when not suspected, in much the same way as the Wassermann test brings to light a totally unsuspected syphilitic infection. Hope has arisen for such a test in the reports of rapid iodine decolorization by pellagrous blood[11a,b] as compared to decolorization by non-pellagrous blood. Adequate confirmation of the worth of the reaction is not yet available, but it is strongly to be recommended that adequate attempts be made to evaluate this test.

Another aspect of diagnosis in pellagra concerns the recognition of related disease. I have already discussed secondary pellagra, presumably due to interference by certain diseases with the intake or absorption of the pellagra-preventive factor. Search for such conditions is particularly indicated in patients giving an adequate dietary history. Rectal stricture due to lymphogranuloma inguinale is so frequent in the colored female pellagrin entering the medical wards of Charity Hospital[79a] that on the Tulane Services this lesion is one of the first to be sought. The diagnostic procedures necessary to determine the presence of secondary pellagra include those necessary for the recognition of the lesions already enumerated under Clinical Aspects. It is hardly necessary to add that in the presence of these conditions careful search should be made not only for the typical signs but also for the less characteristic signs of pellagra.

Treatment. Rational therapy in any disease depends largely upon etiology. Should pellagra be infectious in origin, development of specific biologic or chemical agents for its treatment would be most helpful. No such therapeutic agent has been found empirically. Intravenous sodium thiosulphate has been used[63] but without consistent results. Enthusiastic Egyptian reports[54a] have not been confirmed. Similarly other drugs, such as arsphenamine, have been considered specific.[45] In the treatment of neurologic changes massive doses of iron have been used.[6]

The obvious relationship of pellagra to nutritional factors, particularly through the impetus given to such work by Goldberger and his associates, has shown that regardless of cause, nutritional therapy is highly successful. Even so, in patients with severe mental changes a downward course and death may occur in the face of such therapy.

Diet. The well-grounded routine principles of treatment will not be considered here. Prophylaxis in endemic areas depends chiefly upon methods of education of the rural poor to produce foods ensuring a varied and substantial diet. Variety is necessary, including milk, eggs, fresh meats and vegetables. Such changes in dietary habits of large groups are not easy to bring about. To compensate for these difficulties the distribution of dried powdered yeast for general consumption in endemic areas is effective, if only palliative.[83]

Active treatment of the disease rests chiefly on an adequate diet supplemented as the stage of the disease and individual requirements

demand. In less severe cases dietary control alone is sufficient, if well balanced and high in calories (4000 or more daily).[64g] Adequate rest is also essential. Foods high in pellagra-preventive properties should be ensured. These include milk, a quart a day; fresh lean meat, including liver; fresh vegetables, particularly legumes; and other foods as pointed out in the lists compiled by Sebrell.[56a]

More severe cases, especially in the acute phases of the disease, require supplements to the diet and a rigidly outlined program to ensure success. The recently reported program of Spies, Chinn and McLester[67] has been successful not only in the alcoholic pellagra of the North, but also in the endemic variety in the South. It demands adequate professional and nursing care for the effective application of both general and specific measures. Such care is essential for the administration of supportive measures which may mean the difference between success and failure in severe cases. The caloric requirement was raised to 4500 calories, or more, per day with the intake assured by the administration of additional amounts if vomiting and diarrhea interfered. With severe stomatitis, a liquid diet was used until solid food could be taken. All patients were given 180 to 270 gm. of powdered brewers' yeast daily in 20-gm. doses in cold milk. Four patients with severe glossitis, diarrhea, and vomiting were given parenteral liver extract, 20 cc. 4 to 5 times daily, until improvement took place. Symptomatic measures were used as necessary. Under this régime 47 of 50 patients were discharged free from symptoms as compared to mortality rates of 50% or higher elsewhere.

Since pellagra is notoriously a relapsing disease, addition of pellagra-preventing foods to the diet is necessary after hospital treatment. Measures have been enumerated above under Prophylaxis.

Yeast. The dosages of yeast and liver extract used by Spies, Chinn and McLester, as given above, are much higher than those commonly used and recommended. In milder forms of the disease smaller amounts are satisfactory. Goldberger and his associates[33] recommended 15 to 30 gm. ($\frac{1}{2}$ to 1 ounce) of yeast daily, in the form of brewers' yeast. This corresponds to 3 to 6 level teaspoonsful 3 to 6 times daily. Larger doses, approaching those used by Spies *et al.* should be given depending upon the severity of the disease. Yeast cakes and yeast tablets are not satisfactory.[56c]

Liver. Voegtlin[80] reported on the use of liver in pellagra in 1920. Since then there have been many reports on the use of liver and liver extracts.[56c] Much of this work, including that on black tongue, I shall pass over. In 1933, Ramsdell and Magness[52] were successful with intramuscular extract in 2-cc. doses plus good diet. Ruffin and Smith,[53c] in 1934, found liver extracts orally satisfactory, but found little or no improvement with intramuscular injections. These patients were kept on a pellagra-producing diet in both oral and intramuscular studies. Boggs and Padget[10] were successful with both liver diet and oral liver extract. Spies[64c,e] administered liver extract to patients with severe stomatitis and glossitis by the intravenous and intramuscular routes. Doses as high as 80 cc. and 30 cc., respectively, were used and the diet was pellagra-producing. Within 24 hours improvement was noted and in 72 hours the lesions were healed. Ventriculin was also effective. Dosage was much higher than in the negative experiments of Ruffin

and Smith. Later the latter authors[53b] reported that parenteral extracts were effective if given in sufficiently large doses. They pointed out that since most patients with pellagra will recover without supplemental therapy when fed a well-balanced hospital diet, liver preparations can be evaluated only by use on patients who have failed to improve on a basic diet, or who have relapsed after exposure to sunlight.

The efficacy of liver and liver extracts orally and parenterally is obvious from the above reports. Sebrell[56c] points out that liver extracts are prepared and assayed for use in pernicious anemia. Their value in pernicious anemia does not necessarily bear any relationship to their value in pellagra so that large doses are necessary. In general, the oral administration of 75 to 100 gm. of liver extract daily rapidly cures most patients and parenteral liver is necessary only in gravely ill patients and those unable to ingest the proper diet orally. Their use supplements and does not substitute for the principles of dietary treatment already outlined.

Nicotinic Acid. The report of Elvehjem *et al.*,[19] less than a year ago, that nicotinic acid is effective in the cure of black tongue has led to the widespread use in human pellagra of already available commercial preparations. Its isolation from liver suggests that the effectiveness of liver preparations is in a large part due to its presence, and that it may be the P–P factor of Goldberger. Its distribution in foods and correlation with the pellagra-preventive properties of foods is not yet known. The effectiveness of the preparation in black tongue has already been confirmed[15b,46,74] and the cure of a similar deficiency state in pigs is on record.[14]

In human pellagra striking results have been reported.[22,62,68] Patients placed on restricted diets for control periods have shown complete remission on the exhibition of nicotinic acid. The 4 patients of Fouts, Helmer, Lepkovsky and Jukes, and the 17 of Spies, Cooper and Blankenhorn showed healing of mucous membrane lesions within 48 hours. In the former series, all patients showed distinct improvement in general condition within the same period. In 1 patient, diarrhea ceased and stools were normal in 72 hours. In the latter series, glossitis, stomatitis, ptyalism, vaginitis, urethritis and proctitis did not reappear, while the patients received nicotinic acid, but the discontinuance of the drug in 1 patient while still on the pellagra-producing diet resulted in recurrence. In the first series, dermatitis began to heal in the second 24 hours and disappeared more slowly than with treatment with liver filtrate, but improvement otherwise was as satisfactory. In the latter series, erythematous lesions with intact epithelium blanched within 24 to 48 hours, but moist, ulcerated, thickened lesions did not seem to be benefited, nor was peripheral neuritis helped. Porphyrinuria was diminished. They quote Sydenstricker and Joliffe on 6 and 3 cases, respectively, with similar results. Smith, Ruffin and Smith[62] report 1 patient in whom there were dramatic results on the skin lesions and mental symptoms. Mental confusion began to improve after 48 hours and after 6 days the patient was entirely rational. Fouts *et al.* noted a distinct improvement in the mental attitude within 48 hours. The Cincinnati investigators did not evaluate mental symptoms.

All have noted undesirable reactions, such as sensation of heat, tingling of the skin, pruritus and dilatation of the peripheral vessels.

Dosage has varied from 60 mg. to 1 gm. daily. Fouts *et al.* gave 1 gm. daily to 1 patient and 500 mg. daily to the others. Smith, Ruffin and Smith gave 60 mg. daily either intravenously, intramuscularly or orally. The Cincinnati group has used nicotinic acid, nicotinic acid amide, and sodium nicotinate, all with similar results. They point out that the maximal and minimal dosage for oral use has not been determined, but found 500 mg. daily, divided into 5 equal doses, safe and effective in the usual case. Probably a smaller dose will be found to be effective. Intravenously, they successfully used 50 to 80 mg. daily, and 100 mg. if added to a hypodermoclysis.

All three of these reports show that nicotinic acid is effective and easily administered. Harris[36] with Hassam, of Cairo, treated 5 pellagrins and 3 controls with oral doses of one-third gram daily. In all 5 patients the erythema subsided rapidly and in 2 the general condition was improved. The failure of the other 3 to improve generally led him to believe that an absence of nicotinic acid may not be the sole major deficiency in some pellagra-producing diets, which leads us again to the theory of multiple deficiencies. Sydenstricker[75] has seen a relapse following complete remission with nicotinic acid and Spies, Cooper and Blankenhorn had 1 such case. Both were on deficient diets. He states that the enthusiastic reception of the drug is natural and commendable, but fears its exploitation before adequate knowledge of the essential facts is available. He continues that the present evidence strongly favors the assumption that nicotinic acid is the pellagra-preventive factor of Goldberger, but the total number of patients treated is small and the time since treatment was started is short. It is most desirable that a minimum effective dose for cure, maintenance and prevention be determined by controlled observations of experienced investigators and that the indiscriminate use of nicotinic acid be strongly discouraged until this information is available.

It must be remembered that the evaluation of a cure for pellagra involves the maintenance of the patient on a pellagra-producing diet when the substance to be tested is administered. Such diets have been used in reported cases but such a procedure is not recommended in routine treatment. The patient is entitled to the full diet as given above with nicotinic acid used only as a supplement.

Smith, Ruffin and Smith[62] suggest that if nicotinic acid is the pellagra-preventive vitamin, its cheapness would permit its mixture in table salt for prophylaxis in endemic areas, as iodized salt is used in goitrigenous regions. Of this Sebrell[56c] says, "This suggestion appears to be premature because there is no information available on the effectiveness of nicotinic acid in the prevention of the disease and because so little is known about its physiologic action. It has been shown further that the diets on which pellagra develops are also deficient in other respects" —a return to the necessity for a full adequate diet.

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PEDIATRICS.

UNDER THE CHARGE OF

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MENINGITIS IN CHILDHOOD.

A review of the literature of meningitis reveals that there are many microörganismal causes other than the tubercle bacillus, the pneumococcus, the meningococcus, the streptococcus and the influenza bacillus. Some of these bacteria are of rare occurrence in meningitis but are none the less important.

Waszkoutzer[50] states that, in contrast to luetic infection of other organs, luetic meningitis is comparatively rare. Pathologically this is a diffuse or gummatous infiltration of the meninges produced by the treponema. Only in a very limited number of cases in the literature is it justifiable to speak of a leptomeningitis in the narrow sense of the word. As a rule, both soft meninges are inflamed and the underlying brain is also involved in the inflammation.

Bradford and Kelley[7] claim that definite bacteriologic proof is offered in only a few of the reported cases of gonococcus meningitis. The organism should possess in addition to the morphologic and cultural characteristics of the gonococcus, either the proper fermentation reaction or such serologic evidence as a positive complement-fixation test or agglutination test. Of these, the characteristic fermentation test would prove the most reliable. On the same subject, Strumia and Kohlhas[43] state that the involvement of the nervous system by gonococcic infection appears to be rare. There are in the literature only 7 cases besides their own which are beyond question correctly diagnosed. In addition to these there have been reported as gonococcic meningitis 10 other cases in which that diagnosis is probably correct.

All proved cases of gonococcic meningitis occurred in the course of acute gonorrheal infection or during acute exacerbations of chronic gonorrheal infection.

Ravitsch and Washington[34] report a case of meningitis in which the Salmonella suipestifer was found. They state that since 1931 at the Harriet Lane Home in Baltimore there have been 28 cases of infection with this organism; but in a few the suipestifer infection followed some other infection, most often pneumonia. The locations of the infections were varied but in only 1 patient did meningitis occur. They found only 3 cases in the literature. In their case, because the mother had been hospitalized the previous evening with a meningococcic meningitis, antimeningococcic serum was administered intrathecally, although the smear showed no meningococci. The culture, made on admission, grew meningococci on the succeeding day and the initial blood culture grew meningococci. Spinal fluid culture made the following day was sterile, but the second blood culture showed Salmonella suipestifer instead of the meningococcus. On the fourth day the spinal fluid culture yielded Salmonella suipestifer and continued to do so for a number of days. They thought that the secondary infection with the salmonella was due to the gross contamination of the cerebrospinal fluid with blood in the course of lumbar puncture. Mitchell[28] reports another case of meningitis due to a salmonella bacillus. The bacteriologic report on the spinal fluid identified the organism as Salmonella morgani. In reviewing the literature he found only 1 report of meningitis due to this organism and this case terminated fatally. In the Mitchell case, an autogenous vaccine was administered and the infant recovered.

Kutscher[24] reports a case of meningitis in a child in which the spinal fluid showed Bacillus fæcalis alkaligines. His search of the literature for a previous case met with no success. He presents this case because of its rarity and as an addition to the rather limited list of organisms of the Gram-negative group which cause meningitis. The organism was described by W. D. Booker, in 1886, and was recovered by him from a case of cholera infantum. It was a Gram-negative motile bacillus possessing cultural characteristics peculiar to itself. This organism was demonstrated in Kutscher's case of meningitis. Kutscher says that probably every bacterium that is capable of producing general septicemia has at one time or another been found responsible for a case of meningitis. According to him, the more commonly found Gram-negative bacilli include influenza, Koch-Weeks, Morax-Axenfeld, pertussis, Ducrey's tularemia, coli group, cloacæ, lactis aërogenes group, dysentery group, Friedländer's group, typhoid group, chromogenic group, alkaligenes and melitensis.

Black[4] reports a case of meningitis in an infant of 4 months in whom the diagnosis of Brucella melitensis meningitis was made by postmortem examination. He points out that two main modes of transmission of Brucella infection to man are recognized. One of these is by the ingestion of infected dairy products such as raw milk, cream and butter. The other is by the handling of infected livestock, infected tissues or uncooked meats. In his report he does not indicate the manner in which his patient may have become infected. Poston and Thomason[32] also report a case of meningitis due to Brucella melitensis.

Craig and Mackenzie[10] report a case of meningitis due to Bacillus acidi lactici, because of its rarity. They say that there have been only 4 previous reports in the literature, 2 being in new-born infants, 1 in a premature infant at the age of 1 month and 1 in an adult. Incidentally they found only 5 references to this infection in other parts of the body. This is a Gram-negative bacillus belonging to the colon bacillus group. It is found in the intestinal canal and is considered to be a harmless saprophyte without pathogenic significance. It may be found in water and in milk. In discussing the possible modes of entry of organisms into the intracranial cavity the authors enumerate several avenues. One possibility is that of intrauterine transmission from the mother in those cases in which there is a prenatal meningitis or one which occurs during the first days of life. Another source of infection is from an otitis media. Still another atrium is through the lymphatics or by direct extension from a contiguous focus in the nose or the mouth. Premature respirations with aspiration of contaminated amniotic fluid and subsequent passage through the Eustachian tube is another possible source of infection. Finally, the infection may be milk-borne.

Another rare type of meningitic infection was reported by Poston, Upchurch and Booth.[33] In this report of a child with clinical symptoms of meningitis, no bacteriologic diagnosis was possible from the spinal fluid, but on necropsy, material from a subdural abscess gave a Gram-positive bacillus which produced beta hemolysis on blood agar. Morphologically and culturally this organism resembled the new species of listerella.

Meningitis is frequently a secondary condition complicating some other primary infection. In the recent literature, there are several reports of this occurring as a complication of several of the infectious diseases of childhood. Gordon, Litvak and Caronna[20] report 2 cases of streptococcic meningitis, and 1 of sympathetic meningitis accompanying streptococcic abscess of the brain complicating scarlet fever. They say that acute purulent meningitis with scarlet fever may be primary or secondary. The primary type is restricted to instances in which careful search during life or at postmortem fails to reveal any localized source of infection. This is exceedingly rare. It may be even rarer than the literature would indicate, since involvement of the middle ear, sinuses or mastoids which failed to give clinical signs during life may be observed at postmortem examination. The pathways of invasion of the meninges in primary meningitis are through the nasopharynx and along the olfactory filaments by way of the cribriform plate of the ethmoid bone; through the sphenoid sinuses to the meninges; by way of the blood stream or lymphatics, and, according to some observers, through the choroid plexus with the current of fluid that is constantly flowing through the foramina of Luschka and Magendie into the subarachnoid space. Secondary purulent meningitis is usually associated with some localized infection. The channels of invasion of the meninges in this type of meningitis may be through the labyrinth or the tegmen tympani. The infection may also travel by way of the local lymphatics or blood capillaries without any visible continuity between the inflammatory focus and the meninges.

Carlson and Morgan[8] report a case of diphtheritic meningitis and

in a search of the English literature were unable to find such a case, although there were 4 cases found in the German literature. Their case developed following otitis media and mastoid. Klebs-Loeffler bacilli were found in nose and throat cultures and in smears from the spinal fluid.

Faust[13] states that neurologic complications of the common contagious diseases, although only occasionally seen in practice, are not rare. The majority of such complications occur in measles, German measles and mumps. In chicken-pox, they are a much less frequent complication. He reports such a case.

A form of meningitis is encountered in the current literature which is a clinical entity of rather recent recognition. This is called acute lymphocytic meningitis. Viets and Warren[49] say that acute lymphocytic meningitis, now classed as a specific virus disease, may be transient or severe and prolonged, or even fatal. They report examples of all three types. According to their findings, the disease in its most severe form is an encephalitis as well as a meningitis. With the high recovery rate it must be assumed that the degree of encephalitis, in the majority of cases that have been reported, is not profound and that the clinical designation of acute lymphocytic meningitis is still justified.

Toomey[46] describes an epidemic of a disease, the symptoms of which are excruciating headache; anorexia with nausea or vomiting or both; pain in the epigastrium on palpation; a low-grade fever; a throat moderately or severely inflamed; some pain on movement of the head; a total white count perhaps lower than usual, but if normal, usually with a relative increase in the circulatory lymphocytes; negative neurologic signs; a spinal fluid pleocytosis with lymphocytes predominating in the severely affected cases; and a hemolytic streptococcus that was easily isolated from the throats of a small percentage of the cases. He thinks that the lack of glandular involvement, the finding of spinal fluid pleocytosis and the changes in the blood picture are distinctive enough to classify this as a new syndrome and he terms it acute epidemic lymphocytosis.

Baird and Rivers[2] present 65 cases which indicate that not all instances of acute aseptic meningitis are due to the virus of lymphocytic choriomeningitis. The etiologic agent or agents responsible for the cases not so induced are not known. From the records of 3 of the cases of lymphocytic choriomeningitis it seems that certain cases of the disease, because of the extent of the paralysis and sequelæ, do not satisfy the criteria laid down for the diagnosis of acute aseptic meningitis. It is difficult or impossible to differentiate by clinical means alone the cases of acute aseptic meningitis caused by the virus of lymphocytic choriomeningitis from those not produced by this agent. However, the spinal fluid cell counts in the cases studied tend to be higher in the former group than in the latter. Livierato and Simoneto[27] observed 5 patients in whom the clinical picture resembled that of tuberculous meningitis. They report that the duration of the disease varied from 14 to 28 days. The subjective and objective symptoms were temporarily improved by lumbar puncture. All of the patients made complete recovery without residual signs in the nervous system. The cerebrospinal fluid was negative bacteriologically and guinea-pig inoculation for tubercle bacilli also gave negative results. The most

remarkable result of the examination of the spinal fluid was the discrepancy between the number of white cells and the quantity of albumin. The lymphocytes were markedly increased, with a tendency to further progression in this direction, while the albumin was either normal or only slightly increased. Blood cultures and examination of the blood for malaria were negative. Intracranial injection of cerebrospinal fluid into dogs and rabbits gave negative results. Because of these points the authors believe that the disease lies in the class of meningitis close to that of poliomyelitis or epidemic encephalitis.

Dummer, Lyon and Stevenson[12] report their observation in a group of 22 cases manifesting symptoms of benign lymphocytic meningitis. The peak of this small epidemic occurred in the months of July and August. The disease developed in widely separated areas of the community except in 2 instances, so that contact with known patients could not have been responsible for its spread. The characteristic symptoms of the disease were headache, vomiting and abdominal pain. On physical examination, rigidity of the neck and positive Kernig and Brudzinski signs were most frequent. Most of the cerebrospinal fluids contained from 50 to 200 cells, chiefly lymphocytes, and the globulin content was greater than normal in about one-half of the group. The fever was of short duration, and in 19 of the 22 cases the leukocytes of the blood were not increased above normal figures. Recovery was rapid and complete. More than one-half of the group were examined from 6 to 8 months after recovery from the disease but no evidence of residual symptoms and signs, nor of changes in behavior, could be discovered. The mildness of the infection, its epidemic characteristics and the absence of any other disease in the patients or in the community makes the observers suspect that this was a definite disease entity probably of a virus nature.

Noone, Habel and Riggs[30] report 37 cases of epidemic lymphocytic meningo-encephalitis in which there was rapid and uneventful recovery in 36 cases. One patient died. There were headache, fever and vomiting in practically every case. Headache was the most striking symptom. In the spinal fluid examinations, the total cell counts varied so widely that it was impracticable to attempt to average them. The range of cell counts was from 40 to 650 cells. The cells were chiefly lymphocytes.

Glanzmann and Heller[18] point out that there are entirely benign serous and even suppurating meningitides, and for this reason it is advisable to be cautious in rendering an unfavorable prognosis in cases presenting meningitic symptoms. The onset is acute and the spinal fluid shows meningitic changes in that there is an increase in the mononuclear cell elements while the fluid may remain clear as is the case in serous meningitis, or there may be a noticeable suppurative turbidity. Direct examination as well as cultures may reveal that the spinal fluid is sterile. This is known as aseptic meningitis. The course is relatively short, benign and without secondary complications. Etiologic factors in the form of local disorders such as otitis media, sinusitis, pneumonia, and intoxication may be absent. There may be no systemic disease or acute or chronic infection as the cause. This form, according to the authors, develops chiefly in children and occasionally even in nurslings.

Staphylococcus as the cause of meningitis is extremely rare. Bloch and Pacella[6] report a case in a child of 17 days. This was interesting, as the occurrence of staphylococcic meningitis under 1 month of age is very uncommon. The baby had a meningocele in the occipital region which was removed when the infant was 6 days old. The symptoms of his illness appeared 2 days later. Under a scab at the site of the meningocele, thick pus was encountered and showed many Gram-positive cocci in clusters. The patient recovered under sulphanilamide treatment.

Speaking of influenzal meningitis, Huntington and Wilkes-Weiss[23] point out that, according to the usual concept, influenzal meningitis is usually primary. In 10 of their cases it seemed clear that the onset of meningitis was preceded by otitis media or pneumonia, and in some additional instances there were other features of interest in the recent history. In the remaining 40 cases, the meningitis might be considered primary, although many of the patients had concomitant otitis and pneumonia. As regards the diagnosis, the authors emphasize the fact that the presence of Gram-negative bacilli in the spinal fluid is not sufficient, but the diagnosis should be confirmed by culture of the spinal fluid in every instance. In purulent intracranial infection in young children the conventional signs are often absent, and influenzal meningitis is no exception to this rule. Suspicion of meningitis in any unexplained febrile illness of an infant is most justifiable. Extrameningeal lesions such as abscess, pleural effusions, pericarditis, metastatic lesions, osteomyelitis, cellulitis and purpura should be looked for. Either leukocytosis or leukopenia may be present in the case of meningitis. The authors found *H. influenza* in one or more cultures in 16 of 24 blood cultures. Fothergill[15] states that, although *H. influenza* meningitis is supposed to be a rare disease, this is only true in the case of adults. Another point that he brings out is that the mortality rate is very high, being 98% in untreated cases. For the treatment of this infection an antiserum has been produced by the immunization of horses with virulent meningeal strains of *H. influenza*. The serum is given intravenously once a day for the first 2 days in dosages of 30 cc. for an infant and from 30 to 50 cc. for older children. The usual precautions against anaphylactic shock must be taken. It is necessary to give the serum intravenously in order to overcome the bacteriemia which is present. However, this means of introducing the serum is of little or no value in treating the infection in the subarachnoid space because of the very slight permeability of the meningovascular barrier for antibodies. For this, a mixture of antiserum and complement is given intrathecally twice a day as long as it seems necessary. The mixture consists of 2 parts of antiserum and 1 part of complement, and the usual dose is 15 cc. of the former and 8 cc. of the latter. It is allowed to run in by gravity after the spinal fluid has been completely drained off. However, the amount of the mixture injected must be less than the quantity of spinal fluid withdrawn. It is important to elevate the foot of the bed after each intrathecal administration and the position of the patient should be changed frequently in order to facilitate the distribution of the mixture throughout the subarachnoid space. While these injections are usually given by lumbar puncture, they may be injected into the lateral ventricles. More on the same

subject has been reported by Huntington and Wilkes-Weiss,[23b] Silverthorne, Fraser and Snelling,[40] Taylor,[44] Spekter[41] and others.

In reporting a case of pneumococcus meningitis that recovered, Bennett and Meier[3] comment that meningitis of this type has an exceedingly high mortality rate and this is particularly true where it complicates otitic infection. Since 1896 until the time of this report some 50 cases of recovery have been recorded, but before the earlier date there has been no recoveries. The treatment of these reported cases of recovery has been variable, but the majority of them have been treated with pneumococcal serums, intraspinally and intravenously. While this was all that was done in some cases, other treatment was given in other cases. These include injections of gentian violet, Pregl's solution, mercurochrome, autogenous vaccines and urotropin by mouth. Optochin has been used with some success.

Shuller[38] says that pneumococcic meningitis is a disease caused by the pneumococcus and may be primary in the meninges or may be secondary to a pneumococcic infection in some distant organ. Pneumococcic meningitis may present the typical symptoms of any meningitis, or it may be practically devoid of any nervous symptoms. The diagnosis of this type of meningitis depends on the symptoms and upon the evidence obtainable from the spinal fluid. The Gram-positive organism is not always found on the first puncture. In several reports specific type pneumococci were identified. Weil[51] reports a case of meningitis due to Type I pneumococcus which was treated with specific type serum and recovered. Frankmann and Stewart[16] report a case of Type II pneumococcus meningitis which recovered and the authors attribute the recovery to hyperthermia. The hyperpyrexia resulted from the reaction to the infection in the ear and mastoid with which the meningitis was associated. Meningitis caused by Type III pneumococcus resulting in recovery is reported by Steinholz.[42] Hirsch[21] reports a case of primary meningitis due to Type XXII pneumococcus. Coppolino and Gannone[9] report a case of pneumococcic meningitis in 2-day-old infant.

Meningitis due to streptococci is quite common, as will be shown, but the non-hemolytic streptococcus occurs infrequently as the etiologic factor. Hodges[22] reports such a case in which there was also congenital heart disease. It may have been that a septic embolus was thrown off from a thrombus superimposed on the congenital heart lesion. At postmortem, careful search of the endocardium failed to show thrombus, vegetation or scar. It may have spread from infection in the left middle ear. This does not seem likely, as there was no evidence of such involvement, and at postmortem the process was acute and apparently recent. It may have resulted from a blood stream infection from some other source. There was an acute febrile attack with sore throat, back pain and rash some 11 days before the onset of meningeal symptoms and this may have been the source of the infection. Scott and Radbill[37] say that while streptococcic meningitis is a fairly common disease, only a few recoveries are recorded annually. They report a case which complicated mastoiditis. Recovery followed mastoidectomy, the usual supportive treatment and the administration of lyophile convalescent scarlet fever serum intrathecally. Zeligs[54] records 2 cases of streptococcic meningitis in which

there was recovery. He feels that the most important factor in the treatment of meningitis is to provide adequate drainage. In 1 of his cases there was spontaneous drainage of spinal fluid from the nose as a result of a fracture of the skull. In the other, daily injections of air not only removed the intraspinal block and prevented new blocks from forming, but it also displaced fluid from the ventricles and materially aided drainage.

Schillinger[35] feels that the treatment of streptococcic meningitis, which is usually otitic, should be prevention. Each case of otitis should be considered as a potential case of meningitis. In that way extension of the infection can be promptly recognized. Such cases should be relieved of the focus of infection by free surgical drainage when they evidence irritation of the dura or invasion of the blood stream. Furlow and Reynolds[17] describe their method of continuous early drainage of the subarachnoid space by means of a ureteral catheter. In conjunction with this they administer large quantities of fluid.

Litvak and Klughertz[26] express several reasons for the marked increase in recovered cases in recent years from streptococcic meningitis. The early diagnosis of otitic meningitis and early and complete eradication of the macroscopic and microscopic foci of infection is the first reason. Next are improved methods of treatment, such as concentrated scarlet fever antitoxin and sulphanilamide and its derivatives The beneficial results of the use of the various forms of sulphanilamide in streptococcic meningitis are reported by a number of authors, including Trachsler, Frauenberger, Wagner and Mitchell,[47] Anderson,[1] and Godwin.[19]

Blacklock and Griffin[5] say that tuberculous meningitis is the most frequent form of meningitis in children. The primary site of infection in a series of 241 cases under 13 years of age was most frequently thoracic in 73.9%, abdominal in 22.8%, in the cervical glands in 2.1% and unknown in 1.2%. Meningitis following primary thoracic lesions was nearly always due to the human type of bacillus and that following primary abdominal lesions was usually due to the bovine type. According to Turner[48] 5% of patients who die of tuberculosis present a meningeal form of the disease and this is especially true in extrapulmonary infections. Scott[36] states that in 300 autopsies, excluding 9 cases in which brain tuberculomas were found, the meninges showed tubercles in 93 of 225 children less than 10 years of age. Between the ages of 10 and 20 there were 3 among 10, leaving 32 among 65 adults more than 20 years of age. Peterman and Kohn[31] say that it is the almost unanimous opinion that tuberculous meningitis is the most common type of meningitis. From a study of 47 definitely proven cases they found that tuberculous meningitis ranks next in frequency after meningococcic meningitis. The first symptoms to appear were vomiting, change in disposition, anorexia, cough and fever. The cases all terminated fatally and most of them in the third week. It was possible to find tubercle bacilli in the spinal fluid in 78% of the entire series and 91% of the recent series in which a special study of the spinal fluid was done. The Levinson test is recommended as an extremely valuable aid in diagnosis. It was found positive in 82% of the cases.

The meningococcus is conceded first place as the causative factor of meningitis. The literature is filled with reports and studies of this

infection. The frequency of this disease especially in epidemics has stimulated investigations into the occurrence of this organism in the nasopharynx of normal individuals. Silverthorne[39] states that in epidemics high contact carrier rates have been shown. Carriers have also been found during interepidemic periods. In his own study, he found in 1227 swabs from 63 normal healthy adults over a 2-year period 19.8% positive for meningococcus. The swabs were made at practically monthly periods. On these monthly examinations the number of positive individuals varied from 16 to 28%. No less than 41% of the group of 63 were positive at one time or another during the 2-year period. Eleven individuals were persistent, 13 were intermittent and 2 were transient carriers. He examined 11 non-contact carrier strains by the bactericidal and mouse-mucin tests and found 3 to be virulent and 8 avirulent. Carriers of meningococcus possess bactericidal power in their blood to their respective strains, whether these strains are virulent or avirulent. Samples of blood from carriers possess bactericidal power to certain virulent cerebrospinal fluid strains.

Craster and Simon[11] state that a thorough knowledge of the bacteriology, anatomy and physiology of the meninges and the cerebrospinal fluid is essential for the proper early diagnosis and treatment of meningococcus infections, which have a low incidence rate and a high mortality rate. A petechial or purpuric rash may be considered the specific rash of meningococcemia. A purpuric rash accompanies the petechial rash when the condition is fulminating. The rash occurs before the spinal fluid becomes cloudy and before the meningeal signs appear. In many cases meningococci may be demonstrated by a Gram stain of blood obtained by needle puncture of a petechial or purpuric area. A Wright stain of blood from a non-purpuric skin may also demonstrate meningococci. Acute fulminating meningococcemia associated with adrenal hemorrhage is called the Waterhouse-Friderichsen syndrome. In infancy, especially in the first and second years of life, the early signs of meningococcic infection of the meninges do not point to involvement of the central nervous system. They are more likely to suggest an infection of the upper respiratory tract or a gastro-intestinal disturbance. After the disease is well established the stiff neck, the Kernig and Brudzinski signs and other meningeal signs appear.

Levy and Litvak[25] review the findings from a study of 36 cases of meningococcic meningitis. They say that much has been said of permanent damage to the spinal cord and the intervertebral cartilages by lumbar puncture, but they feel that this hazard is small compared with that of a delay in the treatment of a case of meningitis. If there is a reasonable possibility of central nervous system involvement, lumbar puncture should be performed. If the fluid is clear it does not always preclude the possibility of meningitis. The fluid should always be examined carefully. A smear and cell count should be done, a culture prepared and test made for albumin, globulin and sugar. The rule still holds that antimeningococcic serum should be given immediately if a cloudy spinal fluid is obtained. The serum should always be kept in readiness when a lumbar puncture is done in any suspected case. The infants and younger children seldom demonstrate the classical meningeal symptoms and signs. This point cannot be overemphasized. Sometimes meningococci are difficult to culture. Ferry[14] says

that the meningococcus produces a soluble toxin, specific to the various types of the organism, which stimulates the production of homologous antitoxin in susceptible animals. Neutralization of the toxin takes place *in vivo* as well as *in vitro*. Recovery from meningococcic meningitis follows intravenous injections of the antitoxin irrespective of the invasiveness of the organism.

Another new idea in treatment of meningococcic meningitis is recommended by Thompson.[45] This is continuous spinal drainage. While it is physiologically sound it has not gained widespread use because of the technical difficulties. It is most suited for the treatment of meningococcic meningitis where the pus does not tend to become too thick to pass through a cannula as it frequently does in streptococcic and pneumococcic meningitis.

Neal and Appelbaum[29] say that their results with sulphanilamide in meningitis due to the hemolytic streptococcus have been excellent and in pneumococcic meningitis encouraging. Their experience in meningococcic meningitis was too limited for definite conclusions to be drawn, but it is their impression that it is of value in this type of infection. Willien[52] states that the clinical response of the patients to treatment with sulphanilamide was satisfactory in every case in his experience. The possibility of being able to cure meningococcic meningitis by the administration of sulphanilamide by mouth only will be of untold benefit by eliminating the time, trouble and expense of intraspinal and intravenous therapy, together with the elimination of the danger of protein shock and the discomfort of serum sickness. His routine of administration was an initial subcutaneous injection of a large dose of the saturated 0.8% solution in amounts approximating 0.05 gm. per kg. The drug is administered by mouth every 4 hours day and night. The dosage is graduated downward from an upper limit of 15 grains every 4 hours, depending on the size of the patient and the severity of the infection. The drug is continued in reduced dosage for about 10 days after symptoms and laboratory readings have returned to normal. The reason of this is because the drug is bacteriostatic rather than bactericidal. Sodium bicarbonate is recommended grain for grain with sulphanilamide in order to combat acidosis. Magnesium sulphate or sodium sulphate and even sodium chloride are avoided in order to prevent sulphemoglobinemia.

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PHYSIOLOGY

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SESSION OF MAY 16, 1938

A Simple Method for the Determination of Mucin in Gastric Secretion. Harry M. Eberhard and Charles W. Schaffer (Hahnemann Medical College and Hospital, Philadelphia). While doing fractional gastric analyses and duodeno-biliary drainages, one of us has noticed, after examining the samples of saliva recovered during these examinations, that the mucous content of the saliva was totally different from that noted in the gastric juice, bile, feces and so forth. Routine examination of the saliva and other samples by the older methods were too time consuming, so a simpler and more rapid method has been evolved.

The methods generally used and published for the determination of secreted mucin were found lengthy and tedious; extensive investigation with many organic solvents was conducted and it was found that the chlorhydrins were the only water-soluble organic solvents in which mucin at its iso-electric point (pH 3.5) was totally insoluble and readily precipitated.

Pepsin and other proteins of the gastric secretions are not precipitated and are soluble even in the presence of excess chlorides which do not affect the precipitation of mucin. The procedure is simple.

To free it of food particles that are undigested, the sample of gastric contents is filtered through cotton placed loosely in a funnel. To 10 cc. of the gastric secretion are added 20 cc. of ethylene chlorhydrin; shake or agitate to mix thoroughly the chlorhydrin. The mixture is then brought to pH 3.5 by the addition of HCl or NaOH and allowed to stand for about 30 minutes; at the end of this time the mucin is quantitatively precipitated. It may be filtered off and washed on the filter with 65% ethylene chlorhydrin (pH 3.5), dried and weighed; or the pH standardized chlorhydrin solution may be put into a graduated cylinder and the quantity of mucin read directly.

On our gradated "mucinometer" each line represents 10 mg. of mucin. This mucinometer is similar in principle to the albuminometer in which the precipitated protein is read in mg. per cc. volume.

The entire procedure takes 1 hour as against 16 to 18 hours by the ethyl alcohol precipitation, protein hydrolysis and glucose titration method.

We have found that any of the chlorhydrins may be used successfully, but that the ethylene chlorhydrin precipitated the mucin more rapidly. Temperatures of 20° to 25° C. were found most favorable.

Quantitative Emission Spectrum Analysis of Gastric Juice and Allied Problems. A. N. LUCIAN (Randal Morgan Laboratory of Physics, University of Pennsylvania). In this paper were presented the following phases of the subject of spectrum analysis:

1. The advantages presented by quantitative spectrum analysis. Among these were enumerated the following:

(*a*) Very great sensitivity. It was reported that amounts less than 0.000,001% in quantities of the order of a gram were easily detected.

(*b*) Very small quantities are needed for specimens. Liquid specimens of the order of 0.05 to 0.1 cc. were sufficient for analysis.

(*c*) With improved technique, precision of 5% or better can be expected.

(*d*) Many different elements can be determined simultaneously regardless of the dissimilarity of their chemical properties.

2. A discussion of the fundamental physical analysis by the emission spectrum was given. The significance of the *ultimate* or *persistent* lines was brought out.

Brief mention was made of the two well-known standard methods:

(*a*) The step by step comparison method of de Gramont.

(*b*) The internal line standard of Gerlach and Schweitzer. Then a brief discussion of the improved method developed by the author was given. This consisted of obtaining a standard curve for each element (which in all cases so far tried is a straight line) by plotting the density values of the spectrum line or lines of the element, produced by a series of standard solutions, against the known concentrations of the element in question in the various standard solutions, and from such curves reading off the actual amount of the element in question in the unknown samples.

3. A preliminary report of the results obtained was given.

A large number of specimens of fasting gastric juice were obtained under carefully controlled conditions, to minimize the chances of contamination.*

The elements identified in all the specimens were the following: Na, K, Ca, Mg, P, Fe, Cu, Zn, Pb, Mn and C. Other elements were occasionally encountered, notably Sr, Al, and Si.

Referring to the above-mentioned 10 elements (not including C), the following table shows the extreme values of the concentration of these elements ever found in gastric juice specimens investigated in this work.

	Mg. per 100 cc.		Mg. per 100 cc.
Na	53.00–141.0	Cu	0.120–1.80
K	48.00–125.0	Zn	0.150–0.78
Ca	3.00– 19.5	Pb	0.000–0.09
Mg	0.75– 3.5	Fe	0.020–0.10
P	5.80– 13.0	Mn	0.002–0.03

An attempt was made to study the variation in the concentration of a given element with the change in the pH value of gastric juice. As a preliminary report it was stated that as far as the alkali metals, Na, K and Ca, are concerned no definite and consistent trend was noticeable. In contrast, some of the other metals, notably Cu, showed what appears to be a definite trend. A plotted curve indicates that the concentration of copper decreases with increasing values of pH. Further conclusions with regard to this point (concentration *vs.* pH) must await further careful measurements.

Differences Between Castration Cells and Thyroidectomy Cells of the Rat Pituitary in Response to the Administration of Œstrone and of Thyroid Extract. ISOLDE T. ZECKWER (Laboratory of Pathology, University of Pennsylvania). Rats were operated upon at 5 weeks of age and killed 5 weeks later. In each group, some were injected daily with œstrone during the entire postoperative period, the total dosage varying up to 2900 I.U. Others in each group were fed desiccated thyroid extract daily, during the entire postoperative period, the total dosage varying up to 2 gm. The histologic appearance of pituitaries of the treated rats was compared with that of untreated rats. Ninety-four pituitaries were studied.

Complete thyroidectomy was evidenced by characteristic stunting of skeletal growth and inhibition of kidney growth. The effect of œstrone was obvious in the characteristic effects on the gonads. In spite of the known diffuse effects of œstrone in degranulating all chromophile cells, whether the dosage of œstrone was large or small, thyroidectomy cells were abundant in the pituitaries of all thyroidectomized rats. Adequacy of œstrone dosage was proved by its characteristic effect in preventing castration cells in both male and female gonadectomized rats.

The feeding of thyroid extract had no effect on the castration changes in the pituitary when given in doses far in excess of that necessary to prevent the development of thyroidectomy cells in the thyroidectomized rats.

* These specimens were supplied by Drs. Harry Shay and J. G. Cohen of the S. S. Fels Foundation, where this work was carried out.

It is concluded that castration cells and thyroidectomy cells are histologically and functionally different cells, whether or not they arise from different or identical precursor cells.

The Synaptic Excitation of Nerve Cells. D. W. Bronk, M. G. Larrabee, and J. B. Gaylor (Eldridge Reeves Johnson Foundation, University of Pennsylvania). Because the frequency of nerve impulses largely determines their effects, it is important to know how that frequency is modified when the impulses cross a synapse. Recording the response in one or a very few postganglionic fibers (from stellate of cat) while stimulating the preganglionic nerve, we have shown that when the impulses arrive at frequencies corresponding to those which normally occur in the organism, each presynaptic impulse initiates only one postsynaptic impulse.

If, however, the impulses arrive at higher frequencies, there is no longer one synchronized volley of postganglionic impulses for each preganglionic volley. Furthermore, the ganglion cells continue active for some seconds after the end of preganglionic stimulation. Evidence is thus provided for the first time showing conclusively that a train of impulses arriving at a synapse may set up an excitatory state which persists for long duration at a level sufficient to stimulate.

The dependence of synaptic transmission on blood supply has been studied in a perfused ganglion. Certain pathways cease to transmit about 10 minutes after arresting the circulation; all cease to function within 30 to 45 minutes. Recovery has been observed when the circulation is restarted after $7\frac{1}{2}$ hours. The determination of relative rates of failure of conduction over synaptic and purely axonal pathways shows that the synapse does not fail more rapidly than the axone. When conduction is blocked by anemia, the postganglionic cells can no longer be excited by perfusion with acetylcholin. From this, we conclude that loss of irritability of the cell body fails as soon as, if not sooner, than any other part of the synaptic region.

Further Studies on the Mechanism of Kaolin Hypertension. E. Roberts and J. Q. Griffith, Jr. (Robinette Foundation, University of Pennsylvania). This material is a study of hypertension produced in rats by the intracisternal injection of 0.04 cc. of a 25% suspension of kaolin. Following the intracisternal injection in the rat, vascular hypertension occurs by the fifth to twelfth day and pressure tends to fall to normal by the third month. There is increased cerebrospinal pressure. Internal communicating hydrocephalus frequently, though not invariably, occurs in animals surviving a month or more. There is impairment of perineural absorption from the cerebrospinal space into the lymph system but no alteration of absorption into the blood stream. There probably is block in the perivascular spaces leading to the surface of the cortex which may be a factor in the production of hydrocephalus. In long-standing cases the gray matter of the cortex is thinned out of proportion to that seen in another form of hydrocephalus due to cerebellar tumor. Water content of the brain is normal. Blood volume is normal. Minute vessel pressure is increased but falls

in the flare area of a burn. Mean pressure and systolic pressure are both elevated. This hypertension can occur following complete bilateral adrenalectomy. The carotid sinus responds normally to electrical stimulation.

Correction. The statement under "Dosage of the Drug" (AM. J. MED. SCI., **195**, 708, 1938) which read: "In general we have usually given as an initial dose 0.6 gm. per kilo of body weight" should be changed to read: "In general we have usually given as an initial dose 0.06 gm. per kilo of body weight."

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